THE PHYSIOLOGIST

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EDITORIAL

At the Crossroads

Over the course of the last two decades, there have been repeated concerns about the future of physiology. The problem, however, is not the future of the science of physiology itself but rather the future of the discipline or society of physiology. Thus, this long-standing concern has come to focus on the inability of the American Physiology Society to adequately respond to the changing needs of the scientific community and its failure to assure that our meetings provide science at its very best.

It should be noted that the Society, through its publications, has been able to address the evolving needs of the scientific community. However, we must now strive to ascertain that our meetings possess that same scientific quality for which the APS journals are recognized.

In this period of rapid technological expansion and the resultant development of highly specialized areas of research, APS must have the flexibility to sponsor meetings as well as to hold joint meetings with societies that have similar interests. The Society must change its current image of a Society being content with the status quo to one that is on the forefront of science by promoting the best science available.

In light of these developments, the Council of the APS has taken several steps to improve the scientific quality of its meetings. The initial step involved replacing the annual Fall Meeting with one or more specialty meetings (see p. 63). These meetings are sponsored and managed by the APS and can be scheduled at various times throughout the year. The program for the specialty meetings can be planned by one or more sections or by individual members of the Society, who will have the responsibility for the scientific program.

The success of the specialty meetings will depend on the dedication and willingness of members to seek out the active leaders in a given area and to encourage promising young investigators to participate. Again, it is imperative that the goal of each of these meetings is to have the best state-of-the-art science.

The second step taken by Council is more recent and also relates to the scientific quality of the meetings. In 1987, one of the charges from Council to the Long-Range Planning Committee (LRPC) was to make recommendations on how APS should relate to FASEB and other societies, e.g., the Society of Neuroscience, the Biophysical Society, the American Society for Cell Biology, and the Endocrine Society. More specifically, Council wanted an evaluation as to the relationship of FASEB relative to the goals of APS.

In meeting its charge to assess the relation of the APS to FASEB, the LRPC first addressed the usefulness of FASEB as presently organized. It was the view of the LRPC and

The Society must change its current image . . . to one that is on the forefront of science. . . .

Council that an umbrella organization that speaks for and serves a group of scientific societies with kindred interests and objectives is desirable. However, FASEB as currently constituted (six societies) does not and cannot speak for all of experimental biology. It has been recognized for more than a decade that to be effective, FASEB must be enlarged to subserve a larger group than its six founding societies. Despite repeated attempts, this has not been achieved because of constraints imposed by its present governance and financial structure.

Presently, the financial base for FASEB is attained through its assessment to member societies. The per-member assessment for 1989 is projected to be approximately $62.00 per

(Continued on p. 54)

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Deadline for submission of material for publication: Dec. 5, February issue; Feb. 5, April issue; April 5, June issue; June 5, August issue; Aug. 5, October issue; Oct. 5, December issue.

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EDITORIAL *(Continued from p. 53)*

member or $362,886.00 for APS. The per-member assessment covers programmatic activities ($37.45) and supporting services. Programmatic benefits include the *FASEB Journal,* membership directory, and public affairs. The assessments to the societies are normally recovered from the profits of the annual meeting. However, member societies must participate in the meeting to share the profits and recover the assessment. Thus it is obvious that the assessment is a deterrent to the recruitment of additional societies to FASEB. It also restricts member societies from meeting independently of FASEB. Council believes that this restriction is detrimental and restricts the goals of APS.

Since the FASEB Board has not yet formulated a new direction for FASEB, the LRPC recommended that the APS Council go on record urging a restructuring of the organization. The aim of such an action would be to eliminate the constraints on greater representation and ensure the freedom of meeting with other societies.

Based on the LRPC recommendation, the Council endorsed the proposal that a new Federation be constituted that is more representative of the relevant biomedical sciences. At the June retreat in Bethesda, MD, Council adopted the following resolution, which was forwarded to the FASEB Executive Director and Executive Committee.

The American Physiological Society is convinced that the structure of the Federation of American Societies for Experimental Biology (FASEB) (particularly the assessment) limits freedom to organize meetings of the APS and discourages broadening the composition of the FASEB to be more representative of the biomedical community.

The APS believes that a federation of biomedical societies is desirable for promotion of biomedical sciences through public affairs and support services and that such a federation must be broadly representative of the biomedical research community.

For FASEB to attract additional

member societies and to provide the APS with freedom to organize meetings, the assessment must be essentially eliminated. Therefore, the APS requests that the FASEB Board at its 1989 retreat develop a plan to accomplish this by 1994 and communicate the plan to APS prior to the 1990 FASEB Spring Meeting. Based on consideration of this plan, a formal decision will then be made by the American Physiological Society whether to remain a member of FASEB.

To essentially eliminate the assessment, the American Physiological Society recommends that

1. *all FASEB support services operate on a cost-recovery basis;*
2. *the* FASEB Journal *operate on a paid-subscription base;*
3. *the FASEB Public Affairs Office reduce its staff and utilize individual society public affairs officers;*
4. *FASEB establish an endowment fund earmarked for assessment reduction;*
5. *FASEB use income/dividends from existing reserves for assessment reduction.*

These actions of Council are positive and should lead to an increased commitment of APS to the biomedical sciences. The overall success of these steps depend on the involvement and participation of the membership in the scientific affairs of the Society. Active investigators, both young and old, must step forward and provide leadership for APS and thereby ensure a promising future for physiology as well.

Vernon S. Bishop
President

The First Two Years of the FIRST Program

The objective of the First Independent Research Support and Transition (FIRST) Program (R29) is to provide a sufficient period of research support for newly independent biomedical investigators to initiate their research and demonstrate the merit of their research ideas.

It has been two years since the NIH components began making FIRST awards, and the program appears to be well received by applicants and reviewers alike. The following points characterize the program.

- The number of awards has increased from 592 in Fiscal Year (FY) 1987 to 1,238 in FY 1988. Likewise, dollar amounts have increased from $53.4 million in FY 1987 to $108.7 million in 1988.
- The FY 1988 geographic distribution has been quite wide, with 29 states receiving over $1 million each and only 2 states not receiving any R29 awards.
- The approval rates for new R29s were 95.3% for FY 1987 and 96.9% for FY 1988. Corresponding success rates (the number of awards as a percentage of the number of applications reviewed) were 25.4% and 32.4%. These success rates compare favorably with new R01 rates for FY 1987 and 1988.

Data from the table show that

- Younger investigators appear to have been stimulated by the R29 program: 50% of awardees are under 36 years of age as contrasted with 14% for new R01 awardees.
- A higher percentage of females (F) than males (M) has been supported by the R29 than the R01 mechanism: R29, F, 23%, M, 50%; R01, F, 14%, M, 67%.
- A higher percentage of PhDs than MDs has been supported by the R29 than through the R01 mechanism: R29, PhD, 77%, MD, 19%; R01, PhD, 71%, MD, 22%.

TABLE 1. **Demographics on New NIH R01 and R29 Awards, FY 1988**

	New R01		New R29	
	No.	%	No.	%
Degree				
MD	483	22	119	19
PhD	1,594	71	479	77
MD/PhD	114	5	20	3
Other	39	2	9	1
Total	2,230	100	627	100
Gender				
Female	304	14	141	23
Male	1,496	67	372	59
Unknown	430	19	114	18
Total	2,230	100	627	100
Age group				
<31	16	1	25	4
31-35	272	13	271	46
36-40	588	28	238	40
41-45	526	25	53	9
46-50	329	15	7	1
51	377	18	1	0
Total	2,108	100	595	100

Reprinted from *NIH Peer Review Notes.*

American Physiological Society 141st Business Meeting

Time: 5:45 P.M., Wednesday, March 22, 1989
Place: New Orleans Hilton Hotel, New Orleans, LA

I. Call to Order

The meeting was called to order by President Aubrey E. Taylor, who welcomed the members to the 141st Business Meeting of the American Physiological Society. The agenda, the New Members Election Ballot, and the proposed amendment to the Society Bylaws, Article III, Sections 9 and 10 were distributed to the membership along with a list of future Society meetings. President Taylor selected Franklyn G. Knox as parliamentarian.

II. Report on Membership

Vernon S. Bishop, President-Elect, presented a report on the status of the Society membership since the Fall Meeting.

A. Summary of Membership Status

The Society membership reached 6,667 in February 1989, of which 4,764 were regular members, 22 honorary, 211 corresponding, 799 associate, 672 emeritus, and 199 student members (see p. 77).

B. Deaths Reported Since the Fall Meeting

Following the reading of the names of the 20 deceased members, the membership stood for a moment of silence in tribute to their dedication to physiology (see p. 85).

III. Election of Officers and Affairs of the Society

As a result of the election of officers by mail ballot, Martin Frank, Executive Director, announced that the new President-Elect is **Shu Chien,** University of California, San Diego, who will become President on April 6, 1990. **Brian Duling,** University of Virginia, and **Stanley Schultz,** University of Texas, Houston, were elected to Council for three-year terms and **Allen Cowley, Jr.** was elected to complete Dr. Chien's term.

The Society office and staff remain at the disposal of the membership and are glad to interact more closely with members. The major emphasis other than programming, membership, and publications is monitoring the political situation in Washington and interacting with Congressional representatives to assure the continued availability of biomedical and animal research. The membership was sent a brochure listing members of Congress, and members are encouraged to contact their representatives concerning legislative issues affecting animal research and physiology.

IV. Election of Members

A. Appointment of Tellers

President Taylor instructed the membership to strike those names from the ballot for whom they did not wish to vote. Tellers appointed by the President were **Ronald Carlin,** Fairleigh S. Dickinson, Jr. College; **Larry Crawshaw,** Portland State University; **Ronald Korthius,** Louisiana State University; **Harold Modell,** University of Washington; and **Charles Paganelli,** State University at Buffalo.

B. Election of New Members

Following the collection of ballots, President Taylor announced that all candidates on the ballot were elected to membership in the Society (see p. 77).

V. Amendment to the Bylaws

Dr. Taylor announced that the proposed amendment to the Bylaws, Article III. Membership, Section 6 (Associate Corresponding Members) and Section 10 (Nominations for Membership) had been published in *The Physiologist* (31: 156, 1988). This is an important amendment, which extends associate membership to physiologists residing outside The Americas.

A motion was seconded and passed unanimously that the Society Bylaws be amended as presented as follows:

Section 6. *Associate Corresponding Members.* Persons who are engaged in physiology or related fields and/or teaching physiology shall be eligible for proposal for associate corresponding membership in the Society provided they reside outside The Americas. Associate corresponding members may later be proposed for corresponding membership.

Section ~~6~~ 7.
Section ~~7~~ 8.
Section ~~8~~ 9.

APS Council. *Top row, left to right:* C. V. Gisolfi, R. B. Reeves, N. C. Staub, A. W. Cowley, Jr., D. D. Wagner, D. C. Johnson, M. Frank, and B. Bishop. *Front row, left to right:* S. Chien, V. S. Bishop, A. E. Taylor, and H. V. Sparks, Jr.

Section ~~9~~ 10. *Nominations for Membership.* Two regular members of the Society must join in proposing a person for regular corresponding, associate corresponding, honorary, associate or membership. . . .

Section ~~10~~ 11.

Section ~~11~~ 12.

VI. State of the Society

Dr. Taylor said that it is obvious that physiology is alive and well. At the FASEB meeting, our Society presented 2,100 papers and sponsored 196 physiology sessions and 44 symposia, including the very well received debates and mini-symposia.

The chairman of our Finance Committee, **Francis J. Haddy,** presented the Society's finances. The APS is in a sound financial position, ending the year with income over expenses. This income is to be used to initiate new and innovative programs that will benefit the membership and physiology.

The Publications Committee, chaired by **Paul C. Johnson,** began two new journals this year. *AJP: Lung Cellular and Molecular Physiology* will appear in August with **Donald J. Massaro** as editor. The second journal, dealing with physiological teaching, is entitled *Advances in Physiology Education* with **Harold Modell** as editor. In addition, **Neil S. Cherniack** is now the editor of the *Journal of Applied Physiology,* replacing **Alfred P. Fishman.**

Two books, *Clinical Physiology of Sleep* and *Endocrinology: People and Ideas,* were published in 1988. The *Renal Physiology* Handbook and *Hypoxia, Metabolic Acidosis and the Circulation* will be published by Oxford University Press, using the recently stabilized publishing procedure. In addition, **Robert Gunn** is chairman of the Handbook Steering Committee to develop future Handbook series.

Dr. Johnson, who is stepping down as chairman, expressed thanks to the membership for its support during his tenure in which many changes have taken placed. He expressed appreciation to **James A. Schafer,** editor of *AJP: Renal, Fluid and Electrolyte Physiology,* and **Lorne M. Mendell,** editor of the *Journal of Neurophysiology,* each of whom are completing their second three-year terms. He also took the opportunity to thank the many editors, editorial boards, and staff who have made his job easier. What has impressed him with the publications program is the quality of the product. From his perspective, Dr. Johnson has been impressed with the high regard for the publications, both within the Society and outside the Society. He has been equally impressed with the dedication of all the people who are associated with the journals. It indicates not only perseverance and an attitude of hard work but a real love for the journals and books. Dr. Johnson said he was proud to have been a part of the Society's publications program.

Aubrey E. Taylor speaking at the Cajun Festival in New Orleans, LA, at the 1989 APS/FASEB Spring Meeting

Dr. Taylor said that **Allen W. Cowley** presented his first draft of ethical standards for APS, which will be considered at the next meeting of Council. He recommended that members contact Dr. Cowley with their suggestions about ethics. Dr. Taylor believes it is just a matter of time that scientists may be policed at their institutions concerning ethics or misconduct in research laboratories.

The Section Advisory Committee and members of Council will meet in the near future to evaluate the problems arising in section governance and initiatives. This will be most helpful as we strengthen our Council and our Society. The sections are moving along quite well, but it is now time to fine tune them with new objectives and specific aims.

Norman Staub gave Council and our Society an in-depth report on committees and suggested appropriate restructuring and proper charges for all committees.

William Spielman presented the report of the Education Committee with recommendations to establish *1*) APS workshops for Sunday afternoons on technology at very basic levels at the Spring Meetings and *2*) a high school teaching program to be implemented for 1990. Eight high school teachers will be selected to spend the summers in research in physiology departments.

Carl Gisolfi, chairman of the Program Committee, presented a report on the 1990 Spring Meeting. Twenty-two symposia have been accepted and the theme will be "Nervous System Function and Disorders."

The Rochester Fall Meeting program with themes of "Mechanisms of Smooth Muscle Function" and "The Role of Imaging Techniques in Physiological Investigation" is completed. Dr. Taylor is certain this meeting is going to be a real learning experience for all participants.

Finally, the 1990 Fall Meeting in Orlando, Florida has been developed with the theme of "In Search of Physiological Principles: The Use of Animal Diversity and Novel Technology." The meeting format has been developed by our Comparative Physiology Section, under the direction of **Larry Crawshaw,** and several other societies

and sections have shown interest in this exciting meeting.

The Long-Range Planning Committee chairman, **Ernst Knobil,** reported

that he was appointed chairman two years ago at which time the committee was given a charge to *1*) develop a "white paper" on the future of physiology and the ways in which the Society can be useful to the progress of the discipline; *2*) make recommendations on how APS should relate to FASEB and other societies; *3*) develop a plan for more active leadership in the development of programs (the committee should consider the success of the Publications Committee as a model for what may be possible in the area of program); *4*) make recommendations on how the Society can best serve those sections that currently have minimal participation in its meetings; and *5*) make recommendations about the number and characteristics of the meetings of the Society.

Dr. Knobil said that the first charge of developing a white paper on the future of physiology is by far the most substantive. To begin with, the committee had to define physiology, and surprisingly this was not an easy task. Physiology means different things to different people, and of great concern to us is that physiology does not mean anything to some. There seemed to be a consensus, achieved with some difficulty within the committee, that physiology means "regulatory biology" (and all of its dimensions and levels of complexity from behavior to molecular genetics) and vice versa that regulatory biology is physiology. Consideration is being given by the committee and it is being transmitted to Council that the name Regulatory Biology should be added to our current name.

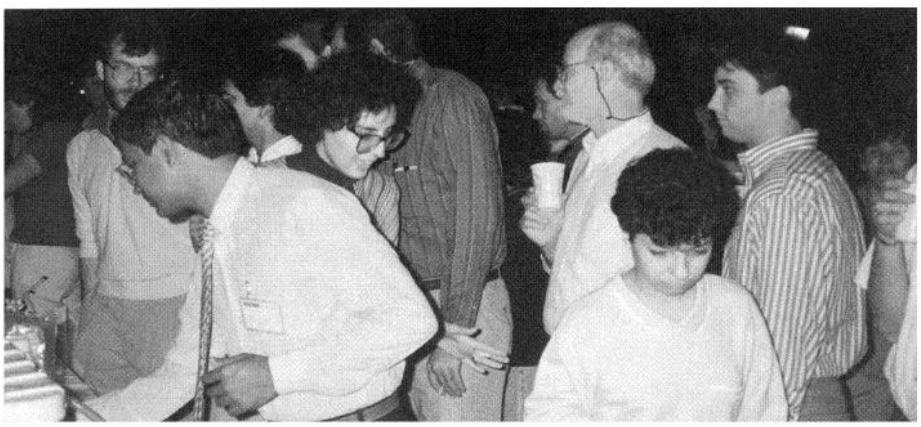
The other problem that confronted the committee at the very outset was to make sure in considering the future of physiology that we distinguish the various aspects of physiology. Physiology as a science, by any measure, is flourishing and exploding at an incredible rate. It is more vibrant today than it has ever been. The difficulty is that much of that wonderful work is not being conducted in physiology departments and that much of it is not called physiology. But the science is alive and well. There is the issue of physiology as a single traditional discipline that can be encompassed by single individuals. That is not so vibrant and probably has not existed as a disciplinary entity for decades. Then there is the physiology encompassed by physiology departments in medical schools. We all know the specific concerns that arena poses. Finally, there is the future of the American Physiological Society and how we, as an organization, can best serve the needs of physiology in all of these dimensions. The committee at the moment is very much engaged in data gathering and is in the study mode. It is beginning to formulate the recommendations it will make to Council.

The committee has commissioned the American Association of Medical Colleges to search its data bases and tell us something about physiologists represented in the medical school physiology departments. That study has just been released. One surprise the committee encountered in the analysis is that during the last decade, contrary to the perceptions that all of us have, there has not been a decline in the number of graduate students entering physiology. Quite the contrary, there has been a gradual increase, with the largest increase in the academic year 1987–1988. Similarly, there has been a gradual increase in the number of full-time and part-time faculty members in the departments of physiology in the United States. Dr. Knobil was encouraged by these statistics.

A nucleus of the white paper has been initiated by the preparation of a discussion paper by Stanley Schultz, which encompasses many of the issues of concern to the Society as they exist today and projected for the next decade or two. By reiteration of discussions of this paper, we hope that it, along with the other findings of the committee and the white paper, will eventually provide a blueprint of where the Society will be going in the next several decades.

Additional recommendations will be made to Council in the near future regarding the role of the sections in the governance of the Society, a matter that has also been addressed by the Section Advisory Committee. In addition, the relations between the APS and FASEB, a concern that has been on our plate for literally decades, will be ingested if not digested at least one more time.

At its first meeting, the committee made a substantive decision to endorse the recommendation of the Program Committee that the number of meetings where Society business is conducted be reduced from two to one meeting a year, although we hope that Council will keep open the question of during which meeting Society business will be conducted, fall or spring. Dr. Knobil said that during the past year, there has been a tremendous amount of activity within the Council and its key committees, and many major changes have been implemented re-



The Cajun Festival, 1989 APS/FASEB Spring Meeting, New Orleans, LA

garding the programs of the Society and its governance. Sometimes he has the feeling that the Long-Range Planning Committee is going to be preempted by the rapid changes being brought about by our very active Society.

In thanking Dr. Knobil, Dr. Taylor said that Council was looking forward to the white paper.

Sarah Nunneley and the Career Opportunities in Physiology Committee have produced a new career brochure that will be available in the near future.

The Government Initiatives Relations Programs Committee (GRIP) sponsored a workshop, "The Law and Animal Care Committees," on Sunday, which was well received.

The Council heard many other reports and all were very positive and informative concerning physiology in the United States and the world. Dr. Taylor expressed personal gratification to the past presidents of the Society and department chairs for writing him letters about their concerns. Basically, they feel that physiology is in good shape and the major message is that the departments of physiology are doing well. Dr. Taylor plans to address these issues in an article to be published in *The Physiologist.*

Recognizing several members who were going off Council, Dr. Taylor expressed appreciation to **Norman Staub** for his dedication and diligent work over a four-year period.

Immediate Past President **Harvey Sparks,** who has devoted the last six years to the Society, is also leaving Council. Hy Mayerson, President of the Society in 1962–1963, once said, "There is nothing that gets paster faster than a past president." Dr. Taylor expressed the Society's appreciation to Dr. Sparks for the initiation of many programs during his tenure. Thanking Dr. Taylor, Dr. Sparks said, "For me in my professional life, the American Physiological Society is my family and it has been wonderful to serve my family over the last few years. I am proud of the progress we have made and am optimistic about the future. I look forward to coming to these meetings for many years to come to enjoy the science and comradeship."

Dr. Taylor expressed thanks to **Francis Haddy** and **Paul Johnson,** who are serving their last year as chairpersons of our two major committees, Finance and Publications, respectively. After 22 years of dedication, **Clifford Barger** is also leaving the Porter Physiology Development Committee. Other chairpersons rotating off committees to whom Dr. Taylor expressed gratitude for their work are **Sarah Nunneley,** Career Opportunities in Physiology; **David Ramsay,** Animal Care and Experimentation; **Robert Berne,** Ray G. Daggs; **Alfred Fishman,** International Physiology; and **Richard Malvin,** Public Affairs.

Dr. Taylor said his presidency was made much easier with the assistance of the excellent staff in Bethesda. The basic feeling of not being President any more is one of sadness and somewhat of disappointment because it seems that things move slowly—but many things have been accomplished and he thanked everyone for making this possible.

VII. Awards and Presentations

A. **Ray G. Daggs Award** (see p. 60)

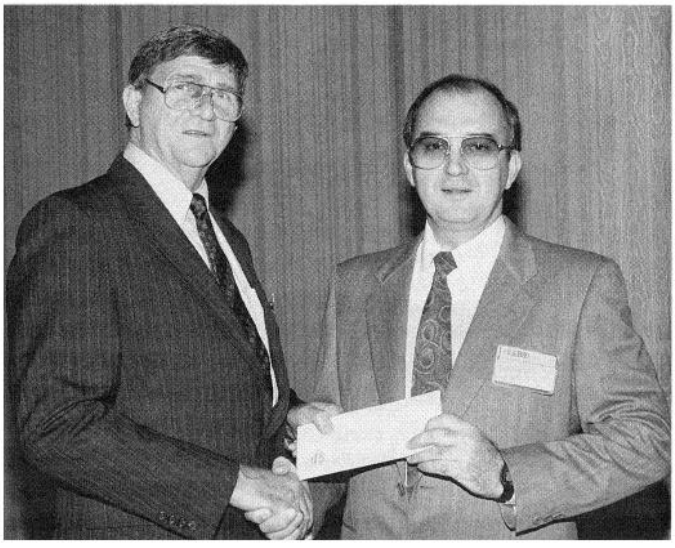
B. **Orr E. Reynolds Award** (see p. 55)

C. **Caroline tum Suden Professional Opportunity Awards** (see p. 82)

D. **Procter & Gamble Professional Opportunity Awards** (see p. 82)

With no new or other business, the meeting was adjourned at 6:30 PM, March 22, 1989.

Vernon S. Bishop
President-Elect



President Aubrey E. Taylor presenting check to Ernest M. Wright of the UCLA School of Medicine, who gave the 1989 Walter B. Cannon Memorial Lecture. The lecture, sponsored by The Grass Foundation, was entitled, "Intestinal Glucose Transport: From Molecules to Man."

1989 Ray G. Daggs Award

The purpose of the Ray G. Daggs Award is to recognize a physiologist who is judged to have provided distinguished service to the science of physiology and to the American Physiological Society. At the 1989 Spring Meeting, Aubrey Taylor, APS President, said, "I can think of no one who fits that criterion better than this year's recipient—**Bodil Schmidt-Nielsen.**

"Unlike most of us who drifted into science during our formative years, Bodil was born to be a scientist. Her parents both were physiologists who ran a small laboratory in Copenhagen. To quote her own words as cited in APS' Centennial History: 'I am the youngest of four children . . . and we children were daily exposed to conversations dealing with topics in physiology. Also, the many visitors and guests who came to the house were mostly scientists. During my first five years of schooling I was educated at home by a private teacher, together with my older sister. This gave us the opportunity to have lunch daily with our parents as they came over to the house from the laboratory.'

"What clearly is evident from her childhood reflection years is that very early in her life a spark ignited a life-long fascination with the medical sciences, particularly the field of physiology. And because of this we and the field of physiology have greatly benefited.

"Bodil's accomplishments include outstanding research concerning renal functions; she has more than 245 publications and abstracts, a book entitled *Urea and the Kidney,* has been elected to numerous scientific and academies, and has received honors from her native Denmark, including an award from the *Prestigious King Christian X* Fund.

"There is yet another accomplishment for which all of us can be proud. It is the fact that the membership elected Bodil Schmidt-Nielsen as President of the American Physiological Society. She was the first, and hopefully not the last, woman to have held that office.

"But I have only scratched the surface of the many achievements garnered by the daughter of August and Marie Krogh.

"The years 1946 and 1947 are memorable times for Bodil. She and her husband Knut and their two children came to the United States at the invitation of Swarthmore College, where they would be research associates. At Swarthmore she worked with gas analysis using Dr. Per F. Scholander's new micromethods.

"In the spring of 1947, she began her studies of water metabolism in kangaroo rats in Southern Arizona. Bodil describes these studies as a milestone in her career. For two summers she and Dr. Laurence Irving worked in the desert with kangaroo rats, pocket mice, and the desert rat. Through this work, it was discovered that these rodents have a remarkable capacity for concentrating their urine in addition to other water conservation mechanisms.

"Bodil's main interests continue to be the physiology of the kidney and the role of the kidney and other excretory organs in regulating the osmolality and volume of extra- and intracellular compartments. Her work has utilized comparative physiological approaches and has involved studies of structure as well as function. She has worked with amoeba, various invertebrates, fish, amphibians, reptiles, birds, and a variety of mammals from extreme habitats.

Bodil Schmidt-Nielsen receiving the 1989 Ray G. Daggs Award from APS President Aubrey E. Taylor

"Her career has not been all research and teaching. She also devoted 40 years to the interests of APS. In 1949 she was elected to membership, and in 1957 she was the recipient of the second Bowditch Lecture Award. She was elected to Council in 1971, becoming President-Elect in 1974 and President the following year.

"She also has served both as a member and the chairperson of the Perkins Memorial Fellowship Committee, the Honorary Membership Committee, and until two years ago she was a member of the committee. Bodil also served as associate editor of *AJP: Regulatory, Integrative and Comparative Physiology.*

"Bodil Schmidt-Nielsen, you have left a remarkable legacy for us to follow, as we and future generations move ahead as researchers and teachers of physiology and as members of the American Physiological Society. It is my singular honor today to present you the Ray G. Daggs Award. There is no one in my mind who is more deserving of this recognition by your colleagues than you."

Accepting the award, Bodil Schmidt-Nielsen said, "It has been an honor, a privilege, and a real pleasure for me to be a member of the APS for 40 years.

"Forty-two years ago I attended my first FASEB meeting with Laurence Irving and Pete Scholander. The total number attending the meetings was 4,000. I was awed and amazed to find that there could be so many physiologists in one country. Although I knew a few, most were unknown to me.

"Since then I have personally come to know many wonderful people associated with the Society, not only the Presi-

Ray G. Daggs Award Recipients

1974	H. H. Brookhart
1975	M. B. Visscher
1976	J. D. Hardy
1977	J. H. Comroe
1978	H. Rahn
1979	J. R. Pappenheimer
1980	J. R. Brobeck
1981	A. C. Guyton
1982	R. W. Berliner
1983	C. L. Prosser
1984	E. F. Adolph
1985	A. C. Barger
1986	D. B. Dill
1987	O. E. Reynolds
1988	H. W. Davenport
1989	B. Schmidt-Nielsen

dents, the Council members, and numerous members but also the staff members such as the executive secretaries, Milton O. Lee, Ray G. Daggs, Orr E. Reynolds, and Martin Frank. I think the elected officers of the Society showed great wisdom in choosing these exceptional individuals. I probably had the most direct contact with Orr Reynolds, who came on board the same year as I was elected to Council and with whom I had a wonderful working relationship while I was President. Also, the publications managers, Sara Leslie and Stephen Geiger, were extremely competent and helpful to us authors and became trusted friends.

"What is unique about APS is that its dedication to excellence is combined with such genuine friendliness. This is what has made APS the scientific home for me and many others, far more so than any other society to which I have belonged."

Moving?

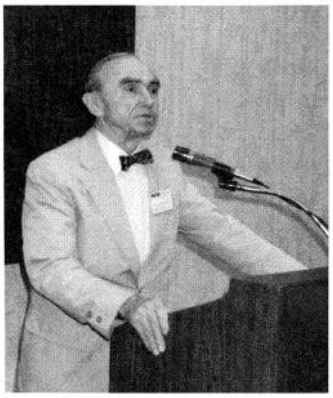
If you change your address or telephone number, please notify the APS office (301-530-7171) as soon as possible.

1989 NIDDK Travel Fellowship Awards

A most successful APS/NIDDK-sponsored Travel Fellowship Program provided an opportunity for 17 highly qualified minority students and scientists to attend the 1989 APS/FASEB Spring Meeting. To enhance their experience at the meeting, the fellows were introduced to mentors at an orientation reception on Sunday evening. Throughout the week, the mentors assisted the fellows in selecting appropriate scientific sessions. NIDDK provided the fellows with information about minority support programs at NIH during a workshop conducted by Dr. Tony Demsey. The American Cyanamid Company once again sponsored the luncheon, held on the last day of the meeting. Dr. David L. Crandall addressed the group about opportunities for minorities in the pharmaceutical industry. Dr. A. Clifford Barger also addressed the group as retiring Cochair of the Porter Physiology Development Committee.

Spring 1989 Fellowship Recipients were Della Bewernick-Montion (California State University, Los Angeles); George T. Blevins, Jr. (University of Arkansas for Medical Sciences); Dr. Cheryl Bliss (New York State College of Veterinary Medicine); Dr. Clive G. Charlton (Meharry Medical College); Marina Chicurel (Harvard University); Claude Davis (Tuskegee University); Dr. Ruben Garcia (University of Puerto Rico School of Medicine); Michael E. Lozano (St. Mary's University, Texas); Blanca Ortiz (California State University, Los Angeles); Lorelei Ellazar Perez (Boston University); Marilys G. Randolph (Howard University College of Medicine); Gloria Jean Respress (Dillard University); Maria L. Ruiz (Harvard University); Dr. Priscilla Sanabria (University Central Caribe School of Medicine); Dr. Belay Tesfamariam (Boston University Medical Center); Cheryl Torrence-Campbell (Meharry Medical College); and Alice R. Villalobos (University of Arizona Health Science Center).

David L. Crandall

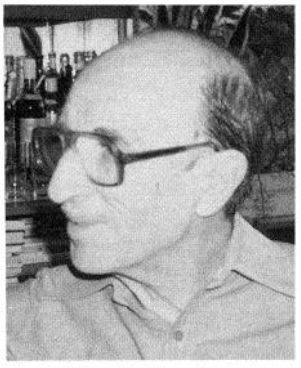


A. Clifford Barger

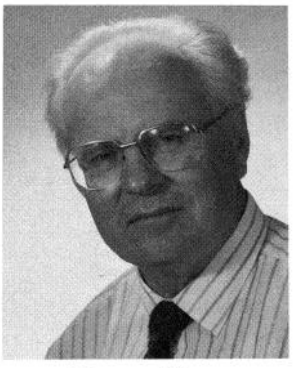
NIDDK Award Winners

Honorary Memberships Granted to Crone, Gazenko, Piiper

Christian Crone



Oleg G. Gazenko



Johannes Piiper

Honorary memberships have been granted to three noted physiologists, each of whom has actively participated in the affairs of the Society for several years.

The memberships were conferred on **Christian Crone, Oleg G. Gazenko,** and **Johannes Piiper.** Honorary membership in APS is limited to distinguished scientists who have contributed to the advances of physiology and do not live in the United States.

•

Crone, who is professor of physiology and biophysics at the University of Copenhagen, is noted for his work in microvascular physiology. He developed methods for quantifying capillary permeability with single-injection techniques. Crone also discovered that D-glucose enters the brain by a facilitated transport mechanism, allowing it to bypass the blood-brain barrier.

Recently Crone developed electrophysiological techniques for quantifying electric conductance of the wall of single microvessels. Along with his colleagues Crone has proposed alternative roles for endothelial vesicles, and currently he is studying single ion channels in endothelial cells.

Crone, who earned both his MD and PhD degrees at the University of Copenhagen, is the recipient of more than two dozen professional honors, awards, and appointments. Although his career has been exclusively with the University of Copenhagen, he has held visiting professorships in France, Canada, and at the Mayo Foundation.

•

Gazenko, who was elected this year to the Soviet Parliament, is one of the founders of space biology and medicine in the USSR. He is a full member of the USSR Academy of Sciences, a USSR State Prize winner, and a retired lieutenant general of the USSR Medical Corps.

He earned his medical degree in 1941 at the Moscow Medical Institute and served during World War II as a flight surgeon. After the war he worked in the Moscow Research Institute of Aviation Medicine investigating psychophysiology of pilots in various environmental extremes.

Gazenko was actively involved in Soviet research projects performed on the earth's first biological satellite and in the preparation for the first man-in-space flights. He also was in charge of the medical support for many of the Russian manned space flights.

In 1969 he was named director of the USSR Ministry of Health's Institute of Biomedical Problems, a post he held for 19 years. The Institute was responsible for the development of methods for stimulating the effects of microgravity on the earth. Gazenko directed a number of experiments in real and simulated spaceflights that helped describe different stages of microgravity, its adverse effects on humans, and the development of countermeasures to be used during and after flight.

He also initiated and directed research projects conducted during the Cosmos space flight series involving biological satellites. The satellites flew both plants and animals as a means of finding the answers to questions relating to space biology and medicine.

•

Piiper, who is the director of the department of physiology at the Max Planck Institute for Experimental Medicine in Göttingen, FDR, was born and educated in Tartu, Estonia, but was separated from his family during World War II. After the war he arrived in Göttingen as a refugee and was admitted to the Göttingen University medical school.

He joined the Max Planck Institute to complete his dissertation for his medical degree and has worked there ever since. In 1958 he was a research fellow with Hermann Rahn at the University of Buffalo, where "he [Rahn] not only introduced me to modern pulmonary physiology, but revived my interest in comparative physiology that had been implanted by my father who was professor of zoology at Tartu University. Since that time my research interest has been divided between pulmonary gas exchange, tissue respiration, and comparative physiology."

APS Specialty Meetings

For several years the American Physiological Society has been transforming its Fall Meeting from one encompassing all aspects of physiology to one embracing selected themes. From 1985 through 1987 the meetings had multiple themes, and in 1988 the Program Advisory Committee endorsed a program with a single theme. The 1989 meeting offers the most focused program to date, featuring the theme "Mechanisms of Smooth Muscle Function." It will be held in Rochester, Minnesota on October 14-19, 1989.

The format of the Fall Meeting continues to evolve. In fact, what was once a single meeting designed for all Society members with annual Society events (Bowditch Lecture, Past President's Address) will become multiple meetings for "specialized groups." The Bowditch Lecture and Past President's Address will be held during the Spring FASEB Meeting.

The specialty meetings of the Society will be held anywhere from August through February and will be organized by the different Sections of the Society or by small groups of Society members. Moreover, beginning in 1992, all specialty meetings will be managed by the APS central office staff rather than by FASEB. This means that the organizing committee of a specialty meeting will have the opportunity to participate in the selection of the meeting site. These meetings offer the Society membership the ultimate in programming opportunities. In general, the organizing committee will select the theme, format, abstract categories, method of presentation (slide/poster), and duration of the meeting. The APS office will be responsible for negotiating the site and space allocation for the meeting, advertising the meeting, and managing all financial and logistic aspects of the program. In essence, the Society is simply asking you to help organize a program that presents the best science and it will provide the space and resources to support you. What more could you possibly ask?

Listed below are more specific guidelines to follow in organizing a specialty meeting of the APS. Any questions regarding the organization of such a meeting should be directed to Dr. Carl. V. Gisolfi, Physiology & Biophysics Department, University of Iowa, Iowa City, IA 55242, or to Martin Frank at the APS Office.

Scope

These meetings should focus on a circumscribed area of physiology. A concerted effort should be made to achieve as much integration as possible, not only between overlapping fields of study but also levels of investigation, i.e., from molecular biology through systemic physiology.

Organizing Committee

The Program Committee should provide direction and assign each section of the Society the responsibility of organizing a specialty meeting. A section may refuse its responsibility or be allowed to organize a meeting during a year that it is not assigned. Each section will form an organizing committee, and the chairperson of that committee will work with the chairperson of the APS Program Committee to develop the framework of the meeting. The chairperson of the APS Program Committee or a small group of members that cross different sections may also organize a specialty meeting. The organizing committee will be responsible for providing APS with *1*) a list of potential meeting sites, *2*) contacts from other societies who may wish to participate in the meeting, and *3*) sources of outside funding.

Abstracts

Submission of abstracts will be left to the discretion of the meeting organizer. There should be a format that provides graduate and postdoctoral students the opportunity to present their data if the material falls within the scope of the theme. Abstracts will be accepted without evaluation and published by the Society. The organizing committee will be responsible for generating a list of topic categories that fall within the scope of the theme.

Location

This will be flexible. Generally, the Society requires at least two years advance notice of proposed meeting sites to book meeting space.

Duration

The meeting should be scheduled for two to three days, preferably over a weekend to take advantage of travel costs.

Management

The APS staff will be responsible for booking site selection, advertisement, setting the registration fee, attracting exhibitors if desired, and solicitation of supporting funds. These meetings will probably require additional staff.

Program Advisory Committee

The PAC will evaluate and contribute to the framework of the meeting. PAC representatives may take basic ideas back to their section membership to ascertain their interest in participating. The PAC will not be allowed to change the primary theme of the meeting.

Publication Policy

Any plan for possible publication should be included by the meeting organizer.

Endorsement Approval

Once the PAC has had the opportunity to evaluate and contribute to the meeting and the Program Committee has

given its approval, the final content will be presented to Council for their final endorsement and approval.

Joint Sponsorship

Sponsorship with other societies will be encouraged.

Number of Meetings

The number of meetings will depend on the needs of the membership of the Society.

Reimbursement Policy

Partial reimbursement for member and nonmember invited speaker expenses may be provided by the Society based on availability of outside funding.

Time of Year

Specialty meetings will be scheduled from August through February (to avoid overlap with preparations for the FASEB meeting).

Carl V. Gisolfi, Chair
Program Committee

APS/FASEB Spring Meeting
Washington, DC April 1–5, 1990

APS Sponsored Symposia

Coronary Collateral Growth and Function. Chair: D. M. Griggs

Regulation of the Coronary Circulation: New Insights From the Microvascular Studies. Chair: W. M. Chilian

Mechanisms of Circulatory Homeostasis: A Tribute to Arthur C. Guyton. Chair: J. E. Hall

Advances in Cardiac Mechanics. Chair: J. W. Covell

Cardiovascular Adaptations to Obesity. Chair: D. L. Crandall

Nonmammalian Models for the Study of Renal Tubule Transport. Chairs: N. Nishimura and W. H. Dantzler

Comparative Physiology of Eicosanoids. Chair: C. A. Herman

Glucose Metabolism, Diabetes and the Vascular Wall. Chairs: N. B. Ruderman, J. R. Williamson, and M. Brownlee

Mechanisms of Prolactin Action. Chair: J. A. Rillema

Regulation of Muscle Carbohydrate Metabolism During Exercise. Chair: C. Stanley

Singular and Interactive Effects of Blood Tonicity and Volume in Dehydration. Chairs: M. N. Sawka and C. E. Wade

Membrane Transport in Physiology: Historical Perspective. Chair: D. C. Tosteson

Cellular Mechanisms of Skeletal Muscle Fatigue. Chair: R. E. Godt

Isoforms of Thin Filament Proteins in Striated Muscle. Chair: R. J. Solaro

Control of the Renal Microvasculature by Vasoactive Peptides. Chairs: P. K. Carmines and J. T. Fleming

Renal and Extrarenal Glutamine Metabolism: Molecular to Organ Level Regulation. Chair: T. Welbourne

Diffusion in Pulmonary Gas Exchange: Models and Experimental Data. Chair: J. Piiper

The Uniqueness of Physiology in the Basic Science Curriculum. Chair: E. Rosenberg

Cytosolic Free Magnesium: Its Regulation and Modulation of Cell Functions. Chair: M. Lieberman

Endothelin. Chair: G. M. Rubanyi

Role of Ca^{2+} Channels and Ca^{2+}-Activated K^+ Channels in Non-Excitable Cells. Chair: W. B. Guggino

Control of Gastrointestinal Hormone Secretion: Physiologic Implications. Chairs: G. H. Greeley, Jr. and G. Gomez

Intrinsic and Extrinsic Neural Control of the Heart. Chair: J. L. Ardell

Amino Acid, Peptide and Protein Transport in the Nephron. Chairs: F. H. Leibach and D. Barfuss

Debate

Sheet and Post Rather Than Tubular Flow in the Pulmonary Microcirculation? Moderator: J. Butler. Pro: S. S. Sobin. Con: W. Guntheroth

Workshop

Instructional Technologies: Design and Production of Interactive Multimedia Programs. Chair: N. C. Anderson

Colloquium

The Emerging Biomedical Scientist: Enthusiastic Optimism or Reason for Concern. Chair: R. D. Carlin (to be scheduled in the early evening)

BMES Symposia

Natural Interfaces Between Biomedical and Biochemical Engineering. Chairs: D. F. Bruley and R. Nerem

Mass Transport in Physiological Systems. Chair: E. V. Cilento

Cellular Bioengineering. Chair: D. A. Lauffenburger

SEBM Symposium

Immunologic Tolerance. Chairs: R. A. Good and R. Billingham

Nervous System Function and Disorders Thematic Symposia

Physiology

Pharmacologic Treatment of Nervous System Trauma (Monday AM). Chairs: S. K. Salzman and A. I. Faddcn

Recent Progress in Neuroendocrinology (Tuesday AM). Chairs: D. K. Sarkar and S. S. C. Yen

Neural Detection of Chemical Signals and the Control of Food Intake (Wednesday AM). Chair: R. C. Ritter

Neural Control of Blood Pressure and Hypertension (Thursday PM). Chair: M. I. Phillips

Gastrointestinal Neurons (Thursday AM). Chair: J. D. Wood

Pathology

Recent Advances in the Understanding of Alzheimer's Disease (Tuesday AM). Chair: R. Katzman

Injury and Regeneration of the Central Nervous System (Tuesday PM). Chair: C. W. Cotman

Nutrition

Recent Advances in Vitamins and Nervous System Function (Tuesday PM). Chair: K. Dakshinamurti and D. B. McCormick

Regulation of Energy Expenditure: The Role of the Central Nervous System (Wednesday PM). Chairs: A. S. Levine and R. J. Martin

The Role of Transport in Regulating Use of Nutrients by the Central Nervous System (Monday PM). Chairs: M. C. McKenna and R. D. Steele

Pharmacology

Activity-Dependent Synaptic Modifications (Wednesday AM). Chair: J. Patrick

Subtypes of Alpha-1 and Alpha-2 Adrenergic Receptors (Wednesday PM). Chair: D. B. Bylund

Behavioral Pharmacology of Abused Substances (Monday AM and PM). Chair: J. H. Woods

Pharmacology of Central Serotonergic Function (Thursday AM). Chair: S. Sparber

Contributions

The American Physiological Society gratefully acknowledges the contributions received in support of the 1989 APS/FASEB meeting from

- Janssen Research Foundation
- Ross Laboratories
- BioLogix Inc.
- Lilly Research Laboratories
- Fidia Research Foundation
- Merck, Sharp & Dohme
- The Jeremy Rill Center
- G. D. Searle & Company
- The Grass Foundation
- Smith Kline & French Laboratories

In Search of Physiological Principles — The Use of Animal Diversity and Novel Technology

American Physiological Society Joint Fall Meeting Orlando, Florida — October 6–10, 1990

Participating Societies:

Canadian Society of Zoologists (CSZ)
- Comparative Physiology and Biochemistry Section

American Society of Zoologists (ASZ)
- Division of Comparative Physiology and Biochemistry
- Division of Comparative Endocrinology

Society of Experimental Biology (United Kingdom) (SEB)
- All Sections

Comparative Respiratory Society

Call for Symposia Topics – Spring 1991

Members are urged to submit proposals for APS symposia to their Section Program Advisory Committee representatives. Organizers should consider multidisciplinary approaches with other sections and the contribution by experimentation at multiple levels of investigation.

What specific questions will the symposium address? Are there two or three conflicting issues that warrant presentation and discussion? What does the symposium offer to the intended audience? Are further directions considered in the material to be presented?

Symposia proposals are welcome for the Spring or Fall Meeting. For the 1991 APS/FASEB Spring Meeting, submit proposals to the appropriate Section Program Advisory Committee representative by January 15, 1990. All proposals should include the following: 1. Title; 2. Organizer and address; 3. Abstract (150 words); 4. Number of half-day sessions; 5. Names of session chairperson(s); 6. Presentors/Discussants – approximately six per half day (list the participant's name and title of presentation as it would appear in the program); 7. Brief biographical sketch (2–3 sentences) of each speaker in the symposium; 8. Budget information – symposia are evaluated on the basis of their scientific merit; however, to coordinate fund-raising efforts by the national office, the anticipated costs to support the travel and lodging of symposia speakers are needed. Organizers will be notified immediately on acceptance of the symposia and given a budget for nonmember participants.

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High School Science Teachers Research in Physiology Program

The American Physiological Society is pleased to announce the initiation of a new program aimed at providing high school science teachers with experience in research in physiology. Recent data have shown that there is a significant drop-off in interest in science, including biology, during the high school years. Because of this decline in interest in biology, fewer students are majoring in the biological sciences in college and going on to advanced degrees in biology. In addition, the general populace no longer has the background in biology that allows them to make informed decisions about important scientific issues such as the human genome project, the greenhouse effect, and the use of animals in biomedical research.

To address this decline in scientific literacy as well as to stimulate more of our young people to enter a career in the biological sciences, the APS, under the auspices of the Education Committee, is embarking on a program to give high school science teachers an experiential education in modern physiology. It is expected that this program will provide teachers with a better understanding of the ways in which research in modern biomedical science is carried out and with a sense of the excitement of science in action. It is hoped that in turn, the teachers will share this knowledge and excitement with their students who will go on to become the physiologists and informed supporters of physiology of the future. The new program is also aimed at encouraging the participation of minority groups in physiology by making a special effort to include high school science teachers who are members of minority groups or who teach significant numbers of minority students.

The High School Science Teachers Research in Physiology Program will be carried out through the awarding of grants on a competitive basis to individual members of the APS. The grants will fund the involvement of a high school science teacher in the research program ongoing in the APS member's laboratory. Grants will be made for up to $5,750, which will include a $5,000 stipend for the high school teacher and $750 to support attendance of the high school teacher at the annual APS/FASEB Spring Meeting. Cost sharing of the teacher's stipend or travel award by the APS member's institution or laboratory will be encouraged but not required. The stipend will support full-time participation of the high school teacher for 10 weeks during the summer.

In addition to participation in research, it is expected that the high school teacher will take part in a variety of activities at the APS member's institution such as seminars, journal clubs, tours, and laboratory rotations. At the APS/FASEB Spring Meeting a special luncheon for the high school teachers and their sponsors will be held during which the high school teachers will share their experiences.

Grant awards will be based on the overall quality of the program planned for the high school teacher, including the level of involvement in the research activities of the laboratory, the background and teaching responsibilities of the high school teacher, the quality of the research program as indicated by publication record and financial support of the APS member, plans for other activities in which the high school teacher will take part, plans for continued interaction between the high school teacher and the APS member or their respective institutions, and an indication of the expected impact of participation of the high school teacher on his/her teaching and school's science program.

Additional information concerning the High School Science Teachers Research in Physiology Program and application forms can be obtained from High School Science Teachers Program, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814.

The APS is committed to improving science education at all levels. The future of the APS and of society in general depends on encouraging young people to enter careers in science and to remain informed about scientific issues. The High School Science Teachers Research in Physiology Program is seen as an important step in improving science education at the high school level. Every member of APS is encouraged to consider participating in this program. APS members should contact high school science teachers in their areas to identify qualified teachers who would be interested in working in their laboratories with support from APS. These contacts may be informal through high school teachers APS members already know and through the teachers of APS members' children, or the contacts may be formal through the local school administration or teacher organization.

High school science teachers will be informed of the APS program through notices in their professional journals and will be encouraged to contact both APS headquarters and local physiologists regarding participation. It is hoped that any members of APS contacted by teachers will be willing and eager to apply to this program. If an APS member would like to take part in the program but does not know of high school teachers who are interested, he/she should contact APS headquarters at the above address or at 301-530-7164 and his/her name will be placed on a list that will be made available to high school teachers expressing interest in the program.

1989–1990 Standing Committees and Sections

APS Council

V. S. Bishop, President
A. E. Taylor, Past President
S. Chien, President-Elect
B. Bishop, Councillor
A. W. Cowley, Jr., Councillor
B. R. Duling, Councillor
G. H. Giebisch, Councillor
S. G. Schultz, Councillor
P. D. Wagner, Councillor
N. R. Alpert, ex officio
C. V. Gisolfi, ex officio
R. B. Reeves, ex officio
W. S. Spielman, ex officio
M. Frank, ex officio

Society Standing Committees

Animal Care and Experimentation

S. M. Cain, Chair (1990)
P. M. Gootman (1992)
H. S. Lowensohn (1991)
R. L. Malvin (1991)
V. M. Miller (1992)
R. A. Murphy (1990)
N. B. Marshall, ex officio (1991)
W. M. Samuels, ex officio
J. Trubatch, ex officio (1992)

Career Opportunities

L. B. Kinter, Chair (1991)
F. G. Hempel (1990)
M. H. Laughlin (1992)
N. H. Manson (1991)
R. S. Moreland (1990)
P. A. Murray (1992)
M. I. Townsley (1991)

Committee on Committees

B. Bishop, Chair (1991)
E. H. Blaine (1992)
E. R. Buskirk (1992)
B. R. Duling (1992)
H. J. Granger (1990)
A. R. Hargens (1991)
L. R. Johnson (1991)
H. A. Kontos (1990)

Committee Reports

Career Opportunities in Physiology

1. Over the past year the committee concentrated on revising the APS brochure used to inform high school and undergraduate students about training and careers in physiology. New material addresses recent developments such as the use of computers and the growing role of molecular biology in physiology. A paragraph on employment opportunities was added to address practical concerns among today's students. The final version of the text was forwarded to the APS office in June, and a consultant is developing artwork to make an attractive brochure that will unfold to make a wall poster. Appeal to a young audience will be further enhanced by including photographs and quotations from several young physiologists with diverse backgrounds. The Society plans to print the brochure in large number for distribution at high school career nights and to mail out in response to inquiries.

2. The committee is also charged with the task of monitoring the supply of new physiologists and the availability of appropriate jobs for them. Data were gathered from three sources: *1*) National Research Council (*Doctorate Recipients From United States Universities,* 1987); *2*) Association of Chairmen of Departments of Physiology (Annual Survey Data); and *3*) APS membership records. Committee members are currently reviewing these data to develop useful analyses and are seeking other sources of relevant information.

3. The third area of committee concern is the development of proposals for career-related presentations at future APS meetings. This was discussed but no action was taken this year.

4. The committee members remain aware of the need to foster good working relationships with the Education Committee, the Liaison With Industry Committee, and with APS efforts to enhance entry into our field by women and minorities.

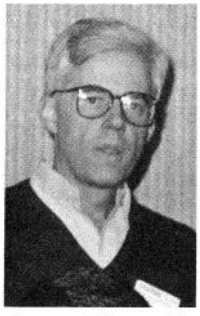
5. The retiring Chair wishes to thank Dr. Martin Frank and the APS staff for their assistance and hopes that the activities of the past two years will help the committee move toward the goal of making more bright young people aware of the variety of good careers offered within the field of physiology.

Sarah A. Nunneley
Chair

Education

The Education Committee met on March 21, 1989 in New Orleans, LA.

1. *High school teachers program.* Last year the Education Committee recommended to Council that the APS support a program for high school teachers to do research in physiology laboratories for a summer. The program was modeled after a similar program sponsored by the American Society of Biochemistry and Molecular Biology (ASBMB). Council sought input from the membership via a survey sent to the departments, which provided evidence of support by the majority of responding departments. Council recommended that this program be implemented for undergraduate-level instructors as opposed to high school teachers. The Education Committee asked the Council to reconsider the program at the high school level because of the opinion that the problem of attracting qualified individuals into biological science must be



approached at a time earlier than the undergraduate level. This recommendation was made to the Council at its meeting of March 22, 1989 and was passed as a formal motion: to support the high school teachers program as originally outlined by Chris Barney for eight teachers at an annual cost of $48,000–$50,000. It is anticipated that the procedure for selection and official announcement will occur in late spring/early summer 1989.

2. *Workshops/symposia.* It was suggested that the planned workshop/tutorial series be offered on Sunday afternoon before the FASEB meeting each spring. It was also suggested that the series be given a name so as to increase its recognition as a permanent offering by the APS at the Spring FASEB Meeting. Jerry Herlihy reported that our first tutorial would be on the subject of "single ion channel experiments" at the FASEB Meeting in 1991. Jerry has been in contact with Stanley Schultz for suggestions of speakers and topics. It was emphasized that this series would be aimed at the nonexpert to provide a mechanism by which that Society member might learn new technologies. Jerry said he would continue to work with Stan Schultz in preparing a proposal for presentation to the PAC at next year's FASEB meeting.

It was also the opinion of the Committee that given the change in the format of the Fall Meeting, it would generally be attended by those particularly interested in the specific theme of the meeting, and therefore the value of such a presentation at the Fall Meeting would be limited. The committee recommended not having such a workshop/tutorial at the Fall Meeting.

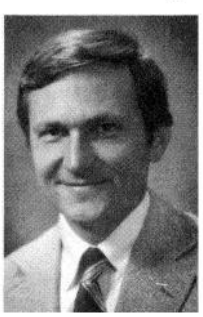
3. *Objectives/curriculum for PhD training in physiology.* The committee discussed its request to the Society sections for a list of teaching objectives. The overall reaction by the various sections was judged to be mixed, but most had responded in such a manner as to indicate that they would be willing to participate in the generation of such a document. Originally the committee requested that each section submit their list of objectives by July 1989, but it is anticipated that many of the sections will need more time to respond. Efforts will be made to try to encourage and help the sections with this request.

4. *Possible development of an APS-sponsored TV program.* Pat Dillon was invited to share with the committee some of his ideas about the possibility of an educational television program about current topics of physiological research. It was decided that the committee would not take action on such a program at the present time but that Pat Dillon would continue to research the possibilities for support. In general the committee was enthusiastic about such an undertaking but considered it to be a major undertaking that is presently only in the early stages of determining feasibility.

William Spielman
Chair

Ethics

The *ad hoc* Committee on Ethics met on March 20, 1989 in New Orleans, LA. The chairman presented for the Committee's review a draft statement of ethical considerations that had been prepared by the chairman with input from the Committee. The purpose of the statement was to develop a framework from which the Society could develop expected standards of conduct for physiologists and a system for dealing with allegations of unethical conduct by a member.



The statement covered the six areas identified by the Committee at its first meeting as possible areas for allegations of misconduct or fraud: publications, conflicts of interests and relationships, treatment of animals and humans, public affairs, grant applications, and students. The statement also covered

R. G. Daggs Award

O. E. Reynolds, Chair (1990)
D. F. Bohr (1991)
W. C. Randall (1992)

Education

W. S. Spielman, Chair (1991)
M. R. Banerjee (1992)
C. C. Barney (1990)
P. C. Churchill (1990)
J. P. Filkins (1991)
L. J. Heller (1992)
M. G. Levitzky (1991)
F. L. Powell, Jr. (1990)
A. A. Rovick, ex officio (1991)

Finance

N. R. Alpert, Chair (1991)
F. G. Knox (1992)
D. W. Rennie (1990)
S. Chien, ex officio (1990)
J. S. Cook, ex officio (1992)
M. Frank, ex officio
J. Liakos, ex officio

Government Relations Initiative Programs

A. W. Cowley, Jr., Chair
T. F. Burks
A. C. Guyton
F. J. Haddy
H. S. Lowensohn
S. Solomon
F. W. Zechman
S. M. Cain, ex officio
J. Trubatch, ex officio

Honorary Membership

R. E. Forster II, Chair (1990)
R. W. Berliner (1991)
W. F. Ganong (1992)

International Physiology

D. B. Jennings, Chair (1991)
C. M. Blatteis (1991)
S. K. Hong (1990)
D. N. Kalu (1992)
L. B. Rowell (1990)
N. L. Stephens (1990)

Liaison With Industry

N. B. Marshall, Chair (1991)
M. P. Blaustein (1991)

Committees (*continued*)

J. W. Fara (1991)
S. F. Flaim (1990)
L. H. Hamilton (1991)
P. M. Vanhoutte (1990)
C. V. Gisolfi, ex officio (1991)
L. B. Kinter, ex officio (1991)
W. S. Spielman, ex officio (1991)

Long-Range Planning

E. Knobil, Chair (1990)
G. H. Giebisch (1991)
J. P. Granger (1991)
J. E. Greenleaf (1990)
R. Lydic (1992)
J. H. Mitchell (1991)
E. R. Nadel (1990)
J. D. Wood (1992)

Membership

C. Levinson, Chair (1990)
N. S. Cherniack (1990)
J. G. Dobson, Jr. (1992)
I. G. Joshua (1990)
R. J. Korthuis (1991)
E. Renkin (1992)
E. G. Schneider (1991)

Perkins Memorial Fellowship

H. V. Sparks, Jr., Chair (1991)
R. F. Grover (1992)
C. V. Paganelli (1991)
N. Sperelakis (1992)
M. P. Hauck, ex officio

Porter Physiology Development

H. M. Goodman, Cochair (1992)
E. L. Ison-Franklin, Cochair (1990)
A. B. Craig, Jr. (1990)
J. C. S. Fray (1990)
P. J. Gunther-Smith (1990)
D. E. Mohrman (1992)
L. G. Navar (1991)
J. G. Townsel (1991)

Program

C. V. Gisolfi, Chair (1991)
J. M. Downey (1992)
R. D. Foreman (1991)
P. D. Harris (1990)
G. A. Hedge (1992)
H. Valtin (1991)
S. Chien, ex officio (1990)

Program Advisory

C. V. Gisolfi, Chair (1990)

Cardiovascular
E. L. Ritman (1991) and
H. J. Granger (1990)

the areas of how allegations are brought to the Society, mechanisms for handling allegations, the role of the Council, and the role of the Society should a member be found guilty of unethical conduct by an investigating agency.

The statement was modified as to the content, order of presentation, and wording.

Allen W. Cowley, Jr.
Chair

Finance

The charge to the Finance Committee at its Spring Meeting is to review and modify the 1989 budget that was presented to Council in October 1988. With the Executive Director, the Committee reviewed the Society's performance in 1988, revised the 1989 budget, and submitted it to the Council for revision and adoption. Based on the performance of the Society in 1988, the Finance Committee recommended an overall budget for fiscal year 1989 of $7,659,886.

During 1988, the Society's journal operations ended the year with income in excess of expenses in the amount of $377,908, a portion of which was directed to the Contingency and Reserve Account. The Society's operating fund, derived from direct membership activities, ended the year with a deficit of $169,871 as a result of Council's decision to write off the slide/tape programs originally produced in the 1970s. The Society's book operations ended the year with expenses in excess of income of $44,476.

The Finance Committee is also responsible for reviewing the performance of the accounts managed by Shearson Lehman Hutton. Over the year, the total value of the accounts was increased by $415,939. As of December 31, 1988, the accounts had the following market value: Operating Reserve Investment Account = $2,694,917; Publications Contingency and Reserve Account = $2,284,327; Caroline tum Suden Account = $279,631; IUPS Account = $187,751; Perkins Memorial Fund = $177,178.

As a result of the review of the Society's finances, Council recommended that domestic journal subscription prices remain unchanged for 1990. Foreign subscription prices, however, will be increased to cover the cost of expedited delivery. In addition, Council allocated $50,000 to support a High School Science Teacher Summer Research Program starting in the summer of 1990. The Finance Committee recommended and the Council approved the transfer from liquid assets of $1,000,000 to the Operating Reserve Investment Account and $400,000 to the Publications Contingency and Reserve Account.

The Publications Contingency and Reserve Fund is a long-term fund established by the publications trustees of which the income can be used by Council for emergencies of the Society including publications. Its utilization is determined each year at the Spring Meeting, keeping in mind that the primary goal is to return as much as possible to capital investment. The Operating Reserve Investment Fund was authorized in 1976. These are funds derived primarily from advance subscription fees received for Society publications; hence, they are diverted from the current operating cash account in an attempt to generate capital gains. Our long-term goal is to have sufficient funds in properly managed accounts to underwrite the activities of APS for one to one-and-one-half years.

The annual audit of APS by Coopers and Lybrand was received and reviewed by the Finance Committee as part of its responsibility. The audit found the operations of the Society to be "in conformity with generally accepted accounting principles" and the statements "present fairly the position of the American Physiological Society."

F. J. Haddy
Chair

APS Balance Sheet, December 31, 1988

ASSETS

Cash, including savings accounts	$1,108,568
Certificates of deposit	3,100,000
	4,208,568
US treasury bills, at cost which approximates market value	2,400,267
Marketable securities, at cost, market value: 1988, $4,979,244; 1987, $4,530,082	4,859,129
Accounts receivable, including $20,000 in both 1988 and 1987 due from FASEB	340,181
Advances to section editors	133,945
Prepaid expenses	32,101
Accrued interest receivable	100,248
Inventories	1,268,549
Deferred audiovisual costs	0
Furniture, fixtures and equipment, net of accumulated depreciation of $63,490	96,131
	13,439,119
Net assets restricted and allocated for unexpended grants and programs:	
Cash, including savings accounts: 1988, $86,507; 1987, $128,651	310,600
Certificate of deposit	100,000
US treasury bills, at cost which approximates market value	144,312
Marketable securities, at cost, market value: 1988, $644,560; 1987, $598,981	588,105
Accounts receivable (payable) net	27,588
	1,170,605
	$14,609,724

LIABILITIES

Accounts payable and accrued expenses, including $73,502 in 1988 and $68,727 in 1987 due FASEB	$329,486
Unearned income:	
Subscriptions	3,801,472
Dues	222,805
	4,024,277
	4,353,763
Unexpended grants and programs	1,170,605
	5,524,368

FUND BALANCES

Publications general fund	6,178,806
Publications special fund	448,378
Society general fund	65,982
Publications contingency and reserve fund:	
Program Endowment Fund	500,000
Principal	1,578,663
Income	313,527
	9,085,356
	$14,609,724

Government Relations Initiative Programs

The Committee on Government Relations Initiative Programs (GRIP) met on March 22, 1989, in New Orleans, LA.

The committee reviewed its annual report, which showed that 8 of its 10 tasks has been completed, including the publication of a booklet telling the membership how to work with Congress and a survey of the membership to determine who had relationships with officials in the Congress and the executive branch of the federal government. Not yet completed were the development of a source book/newsletter and developing a program that would motivate APS members when they are in Washington to visit Congressional offices.

Cell and General Physiology
L. Mandel (1990)
Comparative Physiology
J. Hazel (1991)
Endocrinology and Metabolism
D. Wasserman (1992)
Environmental and Exercise Physiology
E. R. Nadel (1990)
Epithelial Transport Group
D. C. Eaton (1991)
Gastrointestinal Physiology
J. D. Wood (1990)
Nervous System
R. Lydic (1989)
Neural Control and Autonomic Regulation
M. I. Phillips (1989)
Renal Physiology
L. S. Costanzo (1990) and
M. A. Knepper (1992)
Respiratory Physiology
R. A. Klocke (1991)
Teaching of Physiology
R. Carlin (1991)
Water and Electrolyte Homeostasis
G. F. DiBona (1992)
Clinical Physiology Group
J. F. Biebuyck
History of Physiology Group
D. Gilbert (1990)
Hypoxia Group
H. Raff (1992)
MYOBIO Group
J. A Rall
Liaison With Industry
S. F. Flaim
Education
J. T. Herlihy
F. L. Powell, Jr.

Public Affairs Executive

J. Trubatch, Chair (1992)
M. S. Gordon (1991)
S. Solomon (1990)
S. M. Cain, ex officio
N. B. Marshall, ex officio
W. M. Samuels, ex officio

Publications

J. S. Cook, Chair (1992)
F. Abboud (1990)
M. J. Fregly (1991)
C. M. Tipton (1992)
S. H. White (1990)
V. S. Bishop, ex officio
M. Frank, ex officio
B. B. Rauner, ex officio

Section Advisory

B. R. Reeves, Chair (1990)
Cardiovascular
N. R. Alpert (1990)
Cell and General Physiology
P. J. DeWeer (1992)
Comparative Physiology
A. F. Bennett (1991)

Committees (*continued*)

Endocrinology and Metabolism
G. A. Hedge (1990)
Environmental and Exercise Physiology
E. R. Buskirk (1991)
Gastrointestinal Physiology
J. A. Williams (1991)
Nervous System
R. Lydic (1990)
Neural Control & Autonomic Regulation
P. G. Schmid (1991)
Renal Physiology
W. J. Arendshorst (1990)
Respiratory Physiology
R. W. Hyde (1990)
Teaching of Physiology
H. Modell (1990)
Water and Electrolyte Homeostasis
L. Share (1991)

Senior Physiologists

R. O. Greep, Chair (1990)
J. R. Brobeck (1990)
H. C. Davenport (1990)
D. G. Greene (1992)
F. S. Grodins (1992)
S. M. Horvath (1990)

Women in Physiology

S. C. Chew, Chair (1990)
H. V. Carey (1990)
H. J. Cooke (1991)
A. R. Gwosdow (1992)
C. S. Opava-Stitzer (1990)
J. Schwartz (1992)

Society Representatives to Other Organizations

American Association for Accreditation of Laboratory Animal Care

S. M. Cain (1992)

American Association for the Advancement of Science

R. L. DeHaan (1992)
M. I. Phillips (1992)

American Institute of Biological Sciences

M. Frank (Indefinite)

Council of Academic Societies of the Association of American Medical Colleges

S. Gray (1992)
G. A. Hedge (1990)

The report also noted that all four tasks assigned to the Committee on Animal Care and Experimentation had been completed or were near completion, but that only one of the three tasks assigned to the Public Affairs Committee had been started, the other two having been deferred by the committee.

The next item of business was Dr. Ramazzotto's report about the annual meeting of the American Association for the Accreditation of Laboratory Animal Care (AAALAC). After discussing the composition of AAALAC site visit teams, the committee agreed that the Society should develop a roster of its members who are on institutional animal care and use committees and/or who are competent in animal care by training and/or experience, and that the names of these individuals be submitted to AAALAC for use as consultants for site visit teams. It also was suggested that similar actions also should be taken by other organizations such as the American Society for Pharmacology and Experimental Therapeutics and the Society for Neuroscience.

The committee also discussed the feasibility of exploring with appropriate public and private sector agencies the idea of consolidating animal care and use regulation, guidelines, and standards. Dr. Ramsay agreed to draft a statement concerning the issues regarding laboratory assurances, regulations, etc., as well as possible opportunities to explore other issues with private and public sector agencies.

The next agenda item was a review of proposed federal legislation and regulations concerning laboratory animals. The GRIP Committee members were invited to join an Animal Care and Experimentation Committee working party at the APS National Office on May 3 to review and develop the Society's response to proposed regulations to the Animal Welfare Act.

The committee then discussed a proposal developed by a GRIP subcommittee. The proposal recommended that the Society undertake an effort to establish within the NIH an advocacy group supporting animal research. The subcommittee said the advocacy group should be composed of individuals who do research, not the regulators, and that the greatest need for animal research advocates is in support of the large-animal user and where regulations are being written regarding the use and care of laboratory animals.

The subcommittee cited three concerns: *1*) NIH has defaulted on the animal issues and needs a push to do something; *2*) people are trying to legislate animal research out of existence; and *3*) researchers who use mice and rats do not care about what happens to dog research. The subcommittee proposed that the Society get other scientific and educational societies to join with APS to form a committee composed of large-animal users who will write a proposal to be submitted to NIH that states the facts and the need for an advocacy group within NIH that supports large-animal research.

Dr. Ramsay reported that the Society's Animal Care and Experimentation Committee had reviewed earlier the subcommittee's proposal and that its recommendation to GRIP was that the proposal is too global for APS and that NIH, being a federal agency, is not an appropriate advocacy group, but the National Association for Biomedical Research (NABR) could be useful in such an effort. It also was recommended that the development of such a group should first consider the need to amend the Public Health Service's Guide for the Care and Use of Laboratory Animals.

In an unanimous vote the committee directed the subcommittee to rewrite its proposal and submit it to Council with the following recommendations: *1*) APS push for an advocacy group within NIH; *2*) APS seek the support of other scientific and educational societies in this effort; and *3*) if such support is not forthcoming, APS then should go it alone in this effort.

The next item of business was a report on the estimated cost to develop a sourcebook/newsletter that would advise members on where to obtain materials such as video tapes, films, pamphlets, knowledgeable speakers and background information on the animal issues. The production costs per issue would be a mini-

mum of $1,971 for copy preparation (one page, $10 for each additional page), printing, envelopes, labels, inserting, and postage. Personnel costs were not included in the estimate. The Committee unanimously agreed that it be recommended to Council that the necessary funds be made available to develop a sourcebook/newsletter with materials for the book being developed and distributed to the membership at least three times a year.

Fred Zechman reported on the committee's premeeting workshop, "The Law and Animal Care and Use Committees." The workshop had 123 paid registrants and was considered a success and meaningful by those who attended. The question was raised about the $35 registration fee, which was charged to pay for speakers who were not members of APS. William Samuels reported that two APS members had written in protest about the fee and that one non-APS member complained to him at the meeting about the fee.

The Committee unanimously agreed to recommend to Council that the premeeting workshops be continued and that a registration fee be charged to permit the use of nonmember speakers for the workshp programs.

At the previous committee meeting Bill Samuels was asked to explore with NABR the possibility of developing and distributing to public libraries pamphlets telling the need for animal research. He reported that he was informed that neither NABR nor the Foundation for Biomedical Research had the funds for such an undertaking.

The Council asked GRIP for a recommendation as to whether the Society should provide funds for the support of the educational activities of the Association for Animals and Animal Research, a grassroots group at the University of California in Berkeley. It was the Committee's unanimous recommendation that APS not provide financial support for this group because it would set a precedent for APS financial support for other local grassroots organizations.

Arthur Guyton requested that the committee ask the Council to reconsider its policy of supporting increased appropriations for the Animal and Plant Health Inspection Service (APHIS). The Council has supported for more than five years increased appropriations for APHIS to improve the training of its inspectors and reaffirmed its policy last fall after a request from the committee to repeal the policy. The chairman agreed to take the request to the Council for further consideration.

David J. Ramsay
Chair

Porter Development

The report of the Porter Development Committee to the Society again provides the opportunity of informing the members that fellowship funds are available for able minority students at the pre- and postdoctoral level in keeping with the legacy of William Townsend Porter to "encourage and assist more young men and women of promise in the study of physiology." The current predoctoral fellows being supported by the Porter Development Committee are

- J. Michael Gonzalas-Campoy, a candidate for the PhD degree in the Department of Physiology at Mayo Medical School;
- Cynthia Jackson, a candidate for the PhD degree in the Department of Physiology at the University of California at Davis;
- Alfredo Rego, a candidate for the PhD degree in the Department of Physiology at Georgetown University;

Federation of American Societies for Experimental Biology

Board
A. E. Taylor (1990)
V. S. Bishop (1991)
S. Chien (1992)

Executive Committee
V. S. Bishop (1991)

Executive Officers Advisory Committee
M. Frank (Indefinite)

Education Committee
W. S. Spielman (1990)

Finance Committee
F. J. Haddy (1992)

Life Sciences Advisory Committee
W. B. Seevers (1991)

Meetings Committee
C. V. Gisolfi (1990)

Program Committee
M. Frank (Indefinite)

Public Affairs Committee
R. L. Malvin (1991)

Public Information Committee
M. Cassidy (1991)

Publications Committee
L. S. Jefferson (1991)

Research Conference Advisory Committee
D. N. Granger (1990)

3M Life Science Award Committee
W. E. Crill (1990)

National Association for Biomedical Research

M. Frank (Indefinite)

US National Committee on Biomechanics

J. S. Petrofsky (1990)

US National Committee for IUPS

A. E. Taylor (1990)
V. S. Bishop (1991)
S. Chien (1992)
M. Frank, ex officio

Society Sections

Cardiovascular

D. M. Griggs, Chair (1990)
A. L. Mark, Treasurer (1990)
R. J. Traystman, Secretary (1990)
J. Covell, Cardiac Mechanics Subsection
A. P. Shepherd, Splanchnic Circulation Subsection (1988)
H. J. Granger, Program Advisory Committee and Nominating Committee (1990)
E. L. Ritman, Program Advisory Committee (1992)
H. Kontos, Nominating Committee (1989)
J. B. Bassingthwaighte, Nominating Committee (1991)
N. R. Alpert, Section Advisory Committee (1990)

Cell and General Physiology

P. J. DeWeer, Chair and Section Advisory Committee (1992)
C. S. Pace, Secretary-Treasurer (1992)
A. Fabiato, Councillor (1990)
N. K. Wills, Councillor (1991)
L. Mandel, Program Advisory Committee (1990)
M. J. Siegman, MYOBIO

Comparative Physiology

A. F. Bennett, Chair and Section Advisory Committee (1991)
M. H. Bernstein, Secretary (1992)
W. H. Dantzler, Treasurer (1990)
E. J. Braun, Councillor (1994)
J. Hazel, Program Advisory Committee (1991)

Endocrinology and Metabolism

G. A. Hedge, Chair and Section Advisory Committee (1990)
M. H. Goodman, Secretary-Treasurer (1992)
J. L. Kostyo, Councillor (1991)
J. A. Resko, Councillor (1992)
D. Wasserman, Program Advisory Committee (1992)

Environmental and Exercise Physiology

E. R. Buskirk, Chair and Section Advisory Committee (1991)
E. R. Nadel, Secretary/Treasurer and Program Advisory Committee (1990)

- Maria Luisa Ruiz, a candidate for the PhD degree in the Department of Cellular and Molecular Physiology at Harvard Medical School; and
- Pauline Washington, a candidate for the PhD degree in the Department of Physiology at the University of Western Ontario.

In addition, the following postdoctoral fellows are in training with the support of the Porter Development Committee:

- Dr. W. Richard Campbell, a postdoctoral fellow in the laboratory of Dr. R. Clinton Webb, Department of Physiology, University of Michigan;
- Dr. Jean A. King, a postdoctoral fellow in the laboratory of Dr. Eugene K. Emory, Department of Psychology, Emory University; and
- Dr. Annabel Segarra, a postdoctoral fellow in the laboratory of Dr. Bruce McEwen, Laboratory of Neuroendocrinology, Rockefeller University.

The Committee has continued funding for the Atlanta consortium, a program organized with the assistance of the Department of Physiology at Emory Medical School. Two former Porter Development Committee Fellows, Pamela Gunther-Smith and John C. S. Fray, have been Visiting Porter Lecturers in the Atlanta Program. The Dillard Program in New Orleans has been assisted by the staff of the Departments of Physiology at Louisiana State University and Tulane University.

The Committee is also providing support for a Summer Student Research Program for Native American Indians in the Department of Physiology and Biophysics at the College of Veterinary Medicine and Biomedical Sciences at Colorado State University and for a Minority Summer Student Research Program at Michigan State. The Porter Development Summer Research Fellowship Program at the Marine Biological Laboratories at Woods Hole provided support for Yusupha M. Sey in the laboratory of Dr. George M. Langford.

The members of the Porter Development Committee also acted as the selection board for the new Travel Fellowships for Minority Physiologists organized by Martin Frank and supported by the National Institutes of Diabetes, Digestive and Kidney Diseases, which enables minority students to attend the Fall and Spring Meetings of the American Physiological Society.

We again express our appreciation to the Harvard Apparatus Foundation for its continuing support of the Porter Development Program and to the National Institute of Diabetes, Digestive and Kidney Diseases for the Travel Fellowship Award. We also acknowledge gifts from the Lederle Laboratories of the American Cyanamid Company and individual members of the American Physiological Society.

A. Clifford Barger
Eleanor Ison-Franklin
Cochairs

Public Affairs Executive

The Public Affairs Executive Committee (PAEC) met in New Orleans, LA, on March 21, 1989.

The meeting was opened by William M. Samuels, who discussed the US Department of Agriculture's proposed rules for implementing the 1985 amendments to the Animal Welfare Act. Mr. Samuels invited the committee members to participate in a May 3 meeting at the APS national office for the purpose of developing the Society's response to the proposed regulations.

Dr. Malvin then reported on his meeting with Council where he discussed the committee's book project and the need for APS to provide more funds and staff for assisting the committee in its public affairs activities. He reported that the Council said the Publications Committee would review the book project and that

Council would give consideration to providing additional funds and staff for the public affairs program.

The proposed book is to be written for middle school and high school students and would include chapters as to how knowledge evolved out of the use of laboratory animals; the wrongs of the animal rights movement; exhibits as to how the body works; the effects of drug, tobacco, and alcohol abuse on the human body; and dietary considerations, such as salt. The book also would tell of the benefits of a career in science with an emphasis on physiology. Five authors have agreed to prepare the text should the book project be approved by the Publications Committee and Council.

Richard L. Malvin
Chair

Publications

Since the APS Fall Meeting, the Publications Department has continued to respond effectively to the mandated objectives of the Publications Committee and Council: two new journals were launched; the book program continued to develop in its new format on a collaborative arrangement with Oxford University Press; journal production time was decreased; costs were cut; more computerization was introduced into the department; and an agressive promotional campaign was vigorously pursued.

There was a 3% overall increase in pages published by the journals in 1988, although the percentage varied among the journals. The most significant increase was in the *Journal of Neurophysiology,* with 20% (743) more pages.

The number of manuscripts submitted (excluding the new journals) increased by 8% in 1988, which ensures even more published pages for 1989. The most significant increases in new manuscripts received were for *AJP: Heart and Circulatory Physiology* (22%), *AJP: Cell Physiology* (29%), and *AJP: Regulatory, Integrative and Comparative Physiology* (17%). The slowing down of the growth of the *Journal of Applied Physiology* is also significant. Only 1% more manuscripts were received in 1988; in the last 5 years submission of manuscripts had increased from 5% to 10% each year.

Response to the promotional efforts for the new *AJP: Lung Cellular and Molecular Physiology* journal (first issue August 1989) has been encouraging, and by the end of January 1989 there were almost 300 subscribers to the journal; 46 manuscripts have been received. Neil S. Cherniack, editor of the *Journal of Applied Physiology* and Donald J. Massaro, editor of the new journal, are working closely together to transfer any manuscripts sent to *JAP* that would be suitable for the new journal (with author's permission) and vice versa.

A. P. Fishman has accepted the position of consulting editor for the *Journal of Applied Physiology.* He will be handling special articles, commentaries, book reviews, abstracts, and the selection of covers. L. A. Engel has been appointed as internationally based associate editor as of July 1, 1989.

Advances in Physiology Education has received seven manuscripts and there have been over 50 subscriptions sold in response to the promotional campaign so far, through January. Its first issue appears in June 1989.

Subscriptions for all the individual AJP journals increased in 1988 (7% for *AJP: Heart and Circulatory Physiology* and *AJP: Cell Physiology*; 3% for *AJP: Regulatory, Integrative and Comparative Physiology* and *AJP: Gastrointestinal and Liver Physiology*; and 2% for *AJP: Endocrinology and Metabolism* and *AJP: Renal, Fluid and Electrolyte Physiology*). The *Journal of Applied Physiology,*

J. A. Dempsey, Steering Committee (1991)
B. A. Horwitz, Steering Committee (1990)
C. Tipton, Steering Committee (1990)
H. Raff, Hypoxia Subsection (1992)

Gastrointestinal Physiology

J. A. Williams, Chair and Section Advisory Committee (1991)
J. Fondacaro, Secreatary-Treasurer (1991)
J. A. Christensen, Councillor (1990)
P. Rayford, Councillor (1991)
W. A. Weems, Councillor (1992)
J. D. Wood, Program Advisory Committee (1990)

Nervous System

R. Lydic, Chair and Program Advisory Committee (1990)
R. R. Llinas, Section Advisory Committee (1990)
S. M. Barman, Treasurer (1989)
L. A. Campfield, Councillor (1989)
L. T. Landmesser, Councillor (1990)
E. Taub, Councillor (1990)

Neural Control and Autonomic Regulation

P. G. Schmid, Chair and Section Advisory Committee (1991)
C. M. Heesch, Secretary (1990)
M. P. Kaufman, Treasurer (1990)
M. I. Phillips, Program Advisory Committee (1990)

Renal Physiology

W. J. Arendshorst, Chair and Section Advisory Committee (1990)
P. D. Bell, (1992)
T. C. Welbourne, Treasurer (1991)
L. S. Costanzo, Program Advisory Committee (1990)
M. A. Knepper, Program Advisory Committee (1992)

Respiratory Physiology

R. W. Hyde, Chair and Section Advisory Committee (1990)
M. P. Hlastala, Secretary (1991)
N. H. Edelman, Treasurer (1990)
J. R. Rodarte, Councillor (1990)
R. A. Klocke, Program Advisory Committee (1991)

Sections (*continued*)

Teaching of Physiology

H. Modell, Chair and Section Advisory Committee (1990)
K. A. Taubert, Secretary (1992)
D. Richardson, Treasurer (1990)
A. A. Rovick, Education Committee Liaison (1991)
R. Carlin, Program Advisory Committee (1991)

Water and Electrolyte Homeostasis

L. Share, Chair and Section Advisory Committee (1991)
J. E. Hall, Secretary-Treasurer (1990)
G. F. DiBona, Program Advisory Committee (1991)

Epithelial Transport Group

D. C. Eaton, Chair, Program Advisory Committee, and Section Advisory Committee (1991)

History of Physiology Group

J. B. West, Chair (1989)
D. Gilbert, Secretary-Treasurer and Program Advisory Committee
R. H. Kellogg, Member-at-Large (1989)

Hypoxia Interest Group

R. W. Hoyt, Chair (1992)
H. Raff, Secretary and Program Advisory Committee (1992)

MYOBIO Group

M. J. Siegman, Chair (1990)
J. A. Rall, Program Advisory Committee (1991)
R. S. Eisenberg, Steering Committee (1989)
R. L. Moss, Steering Committee (1990)
F. S. Fay, Steering Committee (1989)
A. W. Jones, Steering Committee (1991)
A. Fabiato, Steering Committee (1991)
M. Lieberman, Steering Committee (1989)
R. J. Solaro, Steering Committee (1990)

Physiological Reviews, and the *Journal of Neurophysiology* lost between 1% and 2% of subscribers, and the consolidated *American Journal of Physiology* lost 4%. We are encouraged by the increase in subscriptions to the individual journals and the lessening of decreases for *JAP, PRV,* and *JN,* but the 4% loss of subscriptions for consolidated *AJP* causes concern. A specific promotional campaign is underway for 1989 aimed at those subscribers who dropped the journals. The "drop/add" subscription figures are of interest; e.g., although *AJP: Heart and Circulatory Physiology* increased subscriptions by 7% (or 123), 85 subscribers dropped out. It is those "dropped" subscribers the Society hopes to regain by direct mail approaches. The Society hopes to attract new subscribers by advertisements in appropriate journals and mailings to carefully chosen lists.

NIPS subscriptions have increased by 3%, and we are hopeful an end-of-year promotion will increase that figure.

Newly designed address sheets with advertisements of our journals, books, and activities on the back have not only delivered our journals to the subscribers with a more professional look but are attracting new subscriptions.

A system that reduces production time at the printer by 2 weeks (from 14 weeks to 12 weeks) has been implemented. In addition, accepted manuscripts are entering the system 2 weeks earlier than before for a net reduction in production time of 4 weeks. Because of these new procedures, there is no backlog of manuscripts, a source of pride to the editorial office, which handles 250 accepted manuscripts a month and has 1,000 manuscripts in the production process at any given time. Authors are being encouraged to submit their manuscripts on disk for computerized editing, which saves 35% of typesetting costs per manuscript. The department is continuing to experiment with different methods of production until the most cost-effective system is found without compromising quality. The printers are undertaking more copy preparation of manuscripts for certain journals on an as-needed basis, which has proved of significant benefit during times of sudden staff shortages and influxes of accepted manuscripts. Page-proof correction costs have been cut significantly in the journals by increased standardization of terminology and closer control, more communication by FAX and phone with authors at the manuscript stage, and the development of specialty teams at the printers who only work on APS publications.

Seven interviews have been held by the Publications Committee in the last few months with potential candidates for the editorship of *AJP: Renal, Fluid and Electrolyte Physiology* and the *Journal of Neurophysiology.*

The *Clinical Physiology of Sleep* was published in November with a price of $49 and a pressrun of 1,500; 521 copies were sold by December 31, 1988. The only other book published in 1988, *Endocrinology: People and Ideas* has sold 522 copies in its first 8 months. The four *Handbook* volumes and the final *People and Ideas* volume being completed in-house should all be published in 1989.

The production of the renal physiology *Handbook* and the next clinical physiology book, *Hypoxia, Metabolic Acidosis and the Circulation,* is in the hands of Oxford University Press. They have not yet received all the manuscripts on either book and will not start copyediting until they do.

The Handbook Steering Committee (R. B. Gunn, R. M. Berne, G. A. Hedge, D. G. Stuart, and J. S. Cook, ex officio member representing the Publications Committee) met at APS Headquarters in Bethesda, December 12, 1988. Jeffrey House, vice president of science and medicine of Oxford University Press, and APS staff also attended. They reviewed the APS handbook program and discussed handbooks that needed to be revised and candidates for section and volume editors. Committee members will research topics and candidates and communicate by conference calls. Their recommendations will be forwarded to the Publications Committee for approval. Oxford University Press will then take over all phases of production: signing contracts with editors and authors, copyediting, proofing, manufacturing, promoting, and distributing. Close liaison will be maintained be-

tween American Physiological Society and Oxford University Press under the terms of the original 5-year agreement.

The Technical Book Committee (P. J. DeWeer, Chairman, J. B. Bassingthwaighte, H. E. Morgan, E. M. Wright, and S. H. White, ex officio representing the Publications Committee) met in February to discuss topics and editors for this new series.

The *NIPS* Joint Managing Board met with J. T. Shepherd, editor, and his assistant editors in Rochester to discuss the operation of *NIPS* and the effectiveness of the journal in achieving its goals. B. B. Rauner and M. Frank attended the meeting. Budget, promotion, subsidized subscriptions, and plans for the IUPS Congress in Helsinki were also discussed by the Joint Managing Board. The Board made plans for presenting to the General Assembly of IUPS the proposal to offer *NIPS* to the National Societies for $25 if the Societies buy the journal in bulk for their members (as approved by Council). The Managing Board found the meeting in Rochester to be very productive and commended Dr. Shepherd on the success of the journal under his leadership.

Paul C. Johnson
Chair

Senior Physiologists

The Senior Physiologists Committee serves to help the American Physiological Society maintain an abiding interest in its senior members. All members having reached 70 years of age are identified as "Seniors" regardless of their retirement or emeritus status. In 1988 there were 639 senior physiologists, and an additional 32 members will reach age 70 in 1989.

The names of these senior physiologists are assigned in about equal numbers to the six members of this Committee, and each member maintains contact by mail with his assignees. To this end form letters requesting news of their current interests and activities are sent to members in their 70s and Beaumont House cards are sent to those aged 80 and above. These letters and cards are sent annually for not more than a few years if a response has not been forthcoming. Committee members use their own discretion on this matter.

Over the years the number of senior members responding to our greetings and solicitations averages roughly 20% (or more) of those contacted. In 1987 we had only 19 responses but in 1988 the number increased to 32. This is well within 20%–25% of our mailings. We receive few responses from those well into their 80s and fewer still from those newly retired. The nature of these responses provides an informative cross-section of what senior physiologists do and how they cope with retirement.

Like other chairmen before me I urge (again) that this Committee be made a standing Committee of the APS. There is nothing temporary about the service it renders and there seems to be general agreement that it serves a valuable function. The lack of a woman on this Committee continues to be a source of regret in this era of enlightenment.

Roy O. Greep
Chair

Newly Elected Members

The following, nominated by Council, were elected to membership in the Society at the 1989 Spring Business Meeting, New Orleans, LA.

Regular

Thomas E. Adrian
Creighton Univ.

Zahur Ahmed
SUNY, Buffalo

Steven M. Albelda
Hosp. of Univ. of Pennsylvania

Marcia J. Armstrong
St. Elizabeth's Hosp., Boston

George L. Bakris
Ochsner Clinic, New Orleans

Val R. Beasley
Univ. of Illinois, Urbana

Toby G. Bedford
Univ. of Oregon

Gilbert G. Berdine
Audie L. Murphy VA Hosp., San Antonio

Philip M. Best
Univ. of Illinois, Urbana

Frank A. Blumenstock
Albany Med. Col.

David W. Carley
Univ. of Illinois, Chicago

George H. Caughey
UCSF

Monica M. Caverson
Univ. of Western Ontario

Kirk J. Cureton
Univ. of Georgia

Jonathan M. Davis
Strong Memorial Hosp., Rochester, NY

Randall K. Dupre
Univ. of Nevada, Las Vegas

Paul A. Easton
Univ. of Calgary

Nelson Escobales
Univ. of Puerto Rico

Donald G. Ferguson
Univ. of Cincinnati

Ralph F. Fregosi
Univ. of Arizona

Lourenco Gallo, Jr.
Med. Sch. of Ribeirao Preto,
Sao Paulo, Brazil

Michael H. Golden
Univ. of the West Indies, Jamaica

Christian T. Harker
Oregon Hlth. Sci. Univ.

Fazle Hosain
Univ. of Connecticut

Regular *(continued)*

Sandra Howell
Univ. of Southern California

Randall L. Hudson
Univ. of Illinois, Chicago

Tadashi Inagami
Vanderbil Univ.

Farook Jahoor
Shriners Burns Inst.

Andrew M. Kahn
Univ. of Texas Med. Sch., Houston

Paul L. La Celle
Univ. of Rochester

Dennis C. Marshall
Pfizer International

Thomas R. Martin
VA Med. Ctr., Seattle

Dwight E. Matthews
Cornell Univ.

Owen P. McGuinness
Vanderbilt Univ.

Thomas M. McKenna
Naval Med. Res. Inst.

Paula McKeown-Longo
Albany Med. Col

Mark P. McLean
Univ. of Illinois, Chicago

A. W. Meikle
Univ. of Utah

H. L. Mizelle
Univ. of Mississippi Med. Ctr.

Lyle L. Moldawer
The New York Hosp.

Bryan D. Myers
Stanford Univ. Med. Ctr.

Obi N. Nwasokwa
Harris Chasanoff Heart Inst., NY

Peter R. Oeltgen
Univ. of Kentucky

William H. Percy
Winthrop-Univ. Hosp., Mineola, NY

Robert P. Pittman
Michigan State Univ.

Harrell L. Reed
Naval Med. Res. Inst.

Roberto Refinetti
Univ. of California, Santa Barbara

Peter J. Reiser
Univ. of Illinois, Chicago

Noreen F. Rossi
Wayne State Univ.

David L. Rutlen
Yale Univ.

Timothy W. Secomb
Univ. of Arizona

Sarah A. Shefner
Univ. of Illinois, Chicago

Gerald I. Shulman
Yale Univ.

Message to Members, Section Heads, and Committee Chairs

Appointments to APS Committees

At the recent FASEB meeting in New Orleans I was informed by Council of my appointment as chairman of the Committee on Committees. I view this as an important position and a major responsibility. The output of our Society's committees determines the quality, strengths, and directions of all of our Society's publications, programs, and other activities. The composition of a committee determines the success of that committee in achieving its mandate.

Norman Staub, the previous chairman, did an extremely conscientious and thorough job throughout this three-year tenure. The Society is truly indebted to his dedication and achievements. Among the latter were recommendations for streamlining and improving the Committee's function of advising Council about committee membership and for reviewing the charges given to each committee, a mandate from Council. Staub's recommendations (some of which follow) were unanimously endorsed by Council and will be incorporated in the working procedures of future Committees on Committees.

The purpose of this message is to inform membership of proposed changes in the procedure by which members are nominated for committees and to encourage each member of APS to take advantage of these changes for generating effective, hard-working, productive committees comprised of individuals representing the various sections.

A Past Problem – Solution and New Rules

Problem: In the past people have often been appointed to committees without their knowledge or approval.

Solution: It is now recommended that any person nominating an individual to serve on a committee should contact the nominee and determine whether that individual is willing to serve and is able to devote the necessary time and effort to the job if appointed. Each nomination should be accompanied by a written endorsement from the nominator. The endorsement should provide evidence that the nominee *1)* is actively involved in Society affairs (e.g., frequently attends APS meetings), *2)* is enthusiastic about helping the committee in carrying out its charge, and *3)* has special talents and interests to contribute to the committee's function.

Nominations for committee slots will be accepted at any time throughout the year. The Committee on Committees will prepare recommendations for Council in mid-October. Any nominations received after that date will be held over for consideration the following year.

Self-nomination is very appropriate and welcome. Such a nomination should be accompanied by information about the three points stated above. It is strongly recommended that the self-nominee solicit a supporting letter from another APS member.

Staub Recommendations

1. Members of Council (including the three Presidents) shall not be appointed to committees unless required by APS Bylaws.
2. No members on committees shall be reappointed unless there is a very good reason (e.g., the person is to become chairman or Council requires it).
3. No member shall serve on more than one committee at a time, unless Bylaws or Council requires it (e.g., as liaison or ex officio cross-appointments).

These new rules are expected to broaden the representation of membership on committees, thereby giving more members an opportunity to serve the Society.

Beverly Bishop, Chair
Committee on Committees

Section Reports

Comparative Physiology

At FASEB '89, the Comparative Physiology Section sponsored one slide session, one poster session, and two symposia. The symposia dealt with temperature effects on muscle and locomotor performance and with uptake, synthesis, and functions of organic osmoltyes. The Scholander Award, for the best comparative physiology abstract and presentation by a young investigator, was won by Dr. Jeremy Wasser, who complete his PhD at Indiana University and is doing postdoctoral work at Brown University. The award was presented by Chairman Al Bennett at the Comparative Physiology Section social. Dr. Michael Castellini spoke at the social on his association with Pete Scholander. The Section wishes to thank him for his presentation. It also wishes to congratulate Dr. Wasser and all the Scholander Award contestants in this year's competition for the high quality of their presentations and to thank them for participating.

The Comparative Physiology Section also held its annual business meeting at the FASEB Meeting in New Orleans. Among the issues receiving consideration were programming at the 1990 FASEB Meeting in Washington and at the 1990 Fall Meeting in Orlando. In Washington the Section will sponsor symposia on nonmammalian models of renal function and on comparative aspects of eicosanoids. The Orlando meeting will be held jointly with the Comparative Physiology sections of the American Society of Zoologists and the Canadian Society of Zoologists, as well as with the Society of Experimental Biology (UK) and the Comparative Respiratory Society. The successes of previous joint meetings suggest that the Orlando meeting will be especially exciting. The Section has been assigned responsibility for the meeting's theme, "In Search of Physiological Principles—The Use of Animal Diversity and Novel Technology." Last-minute suggestions for the meeting's program are welcome, as are suggestions for symposia at the 1991 Spring Meeting.

Marvin H. Bernstein
Secretary

Gastrointestinal

The Steering Committee of the Gastrointestinal Section has continued to communicate throughout the year by phone and mail. This year a formal 1½-hour breakfast meeting of the Steering Committee was held at the APS/FASEB Spring Meeting. This was a clear improvement over previous informal meetings held in hotel lobbies. We intend to continue such an annual meeting and would recommend it to other sections. Communication with the membership has included mailing of two newsletters, an election ballot, and the program announcement for our section meeting at FASEB. An annual business meeting was held at FASEB in conjunction with a cocktail reception and the annual awards presentations by the section.

A nominating committee consisting of Helen Cooke, Jack Krier, and Marie Cassidy was appointed to identify two candidates for a three-year position on the Steering Committee. In a mail ballot of primary members, Bill Weems of the University of Texas, Houston was elected. The Steering Committee also gave further consideration of the section bylaws and approved the further revisions requested by the APS. The Committee also judged abstracts submitted for Young Investigator and Travel Awards.

Regular *(continued)*

M. A. Siddiqui
SUNY, Brooklyn

Steven M. Simasko
SUNY, Buffalo

Charles L. Stebbins
Univ. of California, Davis

Marcia L. Stefanick
Stanford Univ.

Barbara Stonestreet
Brown Univ.

Robert F. Taylor
Ball State Univ.

Bryan J. Tucker
UCSD

V. M. Vehaskari
Washington Univ.

William J. Welch
Univ. of Florida

Corresponding

Christopher Ashley
Univ. Lab. of Physiol., Oxford, UK

Guy Atlan
INSERM, France

Rudi F. E. Busse
Univ. of Freiburg, FRG

Jean-William Fitting
C.H.U.V., Switzerland

Musa A. Haxhiu
Rruga e Dubrovnikut, Yugoslavia

David J. Hearse
St. Thomas' Hosp., London, UK

Pierre Lekeux
Univ. of Liege, Brussels, Belgium

Paschalis-Adam Molyvda
Univ. of Athens, Greece

Shigeaki Muto
Jichi Med. Sch., Tochigi, Japan

Ulrich Pohl
Inst. of Appl. Physiol., Freiburg, FRG

Rolf K. Reed
Univ. of Bergen, Norway

Sueko Sagawa
Univ. Occupat. & Environ. Hlth., Kitakyushu, Japan

Akio Sakai
Shinshu Univ. Sch. of Med., Japan

Pompeo Volpe
Univ. of Texas Med. Branch, Galveston

Else K. Hoffmann
Univ. of Copenhagen, Denmark

Noriaki Kondo
Mitsubishi Kasei Inst. of Life Science, Tokyo, Japan

Olatunde E. Okediji
Univ. of Ife, Oyo State, Nigeria

Michael J. Shattock
St. Thomas' Hosp., London, UK

Associate Corresponding

Michael A. Hill
Texas A&M Univ.

Katalin Kauser
Med. Col. of Wisconsin

Lih Kuo
Med. Col. of Virginia

Associate

Susan de Mello Aires
Univ. of Sao Paulo, Brazil

Robert M. Aronson
Univ. of Illinois, Chicago

Douglas L. Ballor
Univ. of Wisconsin, Madison

Joseph W. Barnard
Univ. of South Alabama

William F. Brechue
Univ. of Florida

Ricardo A. Brown
Natl. Insts. on Aging

Frank V. Brozovich
Beth Israel Hosp.

Charles J. Bruce
Yale Univ.

Ronald Bulbulian
Univ. of Kentucky

Carolyn P. Casteel
Univ. of South Alabama

Jon C. Connelly
Univ. of Texas Hlth. Sci. Ctr., Tyler

Thomas A. Davis
Univ. of Florida

Kevin C. Dellsperger
Univ. of Iowa Hosp.

Peter D. Feldman
Univ. of Iowa

Hussein D. Foda
Univ. of Illinois, Chicago

Karen A. Foster
Geisinger Clinic, Danville, PA

Craig C. Freudenrich
Duke Univ.

Andrew J. Ghio
Duke Univ.

Jeffrey M. Gidday
Univ. of Virginia

Robb Glenny
Univ. of Washington

Arthur F. Hagar
LSU Med. Ctr.

Michael A. Hajdu
Univ. of Iowa

Stanley M. Hall
Children's Hosp., New Orleans

C. Terrance Hawk
Univ. of Alabama

Johnson Haynes, Jr.
Univ. of South Alabama

The Gastrointestinal Section sponsored three symposia and a debate at the APS/FASEB Spring Meeting held in New Orleans. The symposia were "Integrative Factors in Gut Function," organized by Sushil Sarna; "Human Colonic Fermentation of Dietary Carbohydrate," organized by Larry Kien; and "Identification, Regulation and Molecular Biology of Epithelial NaCl Transporting Proteins," organized by Mark Donowitz. The debate was entitled "Morass of Terminology in Gastrointestinal Motility." Jackie Wood has solicited topics for future symposia and has presented two symposia titles to the Program Advisory Committee for consideration for the 1990 FASEB Meeting.

The Gastrointestinal Prize for Meritorious Research was awarded to Dr. Ernest Wright, who spoke on "Molecular Biology of Intestinal Transport" at the Gastrointestinal Section Meeting at FASEB.

The Section awarded two Young Investigator Awards for 1989, based on abstracts submitted to the APS/FASEB Spring Meeting. The Predoctoral Award went to Daniel Devor, a graduate student at SUNY, Buffalo, working under Michael Duffey. His abstract was entitled, "Carbachol Induces Oscillations of Membrane Potassium Current in a Human Colonic Secretory Epithelium (T_{84}). The Postdoctoral Award went to Thomas Frieling for his work on "Cellular Neurophysiology of Submucosal Ganglion Cells in the Colon of the Guinea-Pig," carried out at Ohio State University with Jackie Wood. The Section was also allotted one selection for a Proctor & Gamble Professional Opportunity Award. This was awarded to Laura Dunbar-Lewis of the University of Michigan for work carried out in the laboratory of John Williams.

The Steering Committee has considered several new endeavors. Bill Weems will work on a computer link-up for section members so that notices and potentially some newsletters could be distributed electronically. In the programming area we are discussing sponsorship or cosponsorship of a summer conference and/or cosponsoring a fall meeting with a specialty society within gastrointestinal area.

John A. Williams
Chair

Formation of Bioengineering Interest Group

The APS is in the process of formally establishing a multidisciplinary Bioengineering Interest Group and invites any member of the APS who is interested in any aspect of bioengineering, including instrumentation, physiological modeling, control systems, nonlinear dynamics, and fractals, to join. The Biomedical Engineering Society, joining with APS as a guest member of FASEB for the past 14 years, has regularly sponsored symposia and sessions on such topics and will continue to do so. The Interest Group will function within the APS and in collaboration with the BMES where interests overlap. The Group will be a vehicle to broaden the topic areas and will be active at both the Spring and the Fall Meetings. It could also develop FASEB Summer Conferences.

You can join the Bioengineering Interest Group without affecting your affiliation with an APS section. Jim Bassingthwaighte and H. K. Chang are organizing the Interest Group. If you are interested in joining, please write to James B. Bassingthwaighte, MD, PhD, Center for Bioengineering WD-12, University of Washington, Seattle, WA 98195.

Associate *(continued)*

Timothy W. Henrich
Naval Hlth. Res. Inst., San Diego

Larry W. Hunter
Mayo Clinic

Larry P. Krock
USAF Sch. of Aerospace Med.,
Brooks AFB, TX

Michael A. Kurz
Univ. of Iowa

Patrice A. Lee
Oklahoma Med. Res. Fndn.

Thomas M. Linder
Univ. of Washington

Kim E. Longworth
UCSF

Jeffrey B. Madwed
St. Luke's Hosp.

Gerhard Malnic
Inst. of Biomed. Sci., Sao Paulo, Brazil

Susan Margulies
Mayo Clinic

John A. Novotny
Naval Med. Res. Inst.

Mallard D. Owen
Ohio State Univ.

David B. Pearse
Francis Scott Key Med. Ctr., Baltimore

Michael R. Powers
Univ. of Missouri

Robert G. Presson, Jr.
Indiana Univ.

Paulette R. Reimer
Univ. of Arizona

James A. Richardson
Univ. of Tennessee

Mahin Sadre-Mashayekh
Baylor Col. of Med.

Edward S. Schelegle
Univ. of California, Davis

John F. Schmedtje, Jr.
McGuire VA Med. Ctr., Richmond, VA

Lisa M. Schwartz
Univ. of Washginton

J. Keith Smith
LSU Med. Ctr.

Russell F. Stahl
Univ. of Pennsylvania

Lyle G. Walsh
UCLA

Eve L. Warner
New York Med. Col.

Jeremy S. Wasser
Brown Univ.

Margaret V. Westfall
Univ. of Illinois, Chicago

David A. Wiegand
Pennsylvania State Univ.

Student

Mark A. Andrews
Med. Col. of Georgia

Owen R. Carryl
Howard Univ.

Stewart L. Chritton
Mayo Clinic & Fndn.

Joseph F. Clark
Michigan State Univ.

Pieter P. DeTombe
Univ. of Calgary

Linda J. Dieckman
Univ. of Illinois, Chicago

Michael P. Doyle
Univ. of New Mexico

Michael B. Ducharme
Univ. of Toronto

Rehka D. Halligan
Univ. of Texas Med. Sch., Houston

Timothy E. Hewett
Univ. of Cincinnati

Kathleen A. Jarvis
Univ. of California, Davis

Alexandra E. Kemendy
Emory Univ.

Yu Ru Kou
Univ. of Kentucky

Mary I. Leadbetter
Univ. of North Dakota

Robert J. Leadley, Jr.
St. Luke's Hosp.

Christina Leone
Emory Univ.

Timothy Y. Maines
VA Med. Ctr., Charleston, SC

William E. McIlroy
Univ. of Guelph

Elizabeth Ann Montcalm-Mazzilli
USUHS

David M. O'Drobinak
Univ. of Florida

Deborah F. Perlman
Brown Univ.

Gary A. Pritchard
Pennsylvania State Univ.

Roy D. Russ
East Carolina Univ.

Daniel J. Spergel
Univ. of Pennsylvania

Robert C. Tyler
Colorado State Univ.

David H. Vandorpe
Univ. of Ottawa

Stephen J. Warburton
Brown Univ.

Fifty-Year Members

David I. Abramson, 1937
Errett C. Albritton, 1933
Willard M. Allen, 1934
Samuel B. Barker, 1938
Richard J. Bing, 1922
Emil Bozler, 1932
Chandler McC. Brooks, 1933
Paul C. Bucy, 1933
Carl A. Bunde, 1939
Hubert R. Catchpole, 1938
Aurin M. Chase, 1939
Robert W. Clarke, 1936
Charles F. Code, 1939
Madeleine F. Crawford, 1933
Phoebe J. Crittenden, 1937
Ray G. Daggs, 1935
Hallowell Davis, 1925
Louis B. Flexner, 1933
Florent E. Franke, 1934
A. Pharo Gagge, 1937
Robert Gaunt, 1939
Arthur S. Gilson, Jr., 1927
Harold D. Greene, 1936
James B. Hamilton, 1938
Chester W. Hampel, 1936
A. Sidney Harris, 1939
Frances A. Hellebrandt, 1933
Charles B. Huggins, 1932
J. Raymond Johnson, 1939
Jane Sands Robb Johnson, 1925
Joseph L. Johnson, 1934
Frederic T. Jung, 1930
Ancel Keys, 1939
Nathaniel Kleitman, 1923
Irvin M. Korr, 1939
Paul S. Larson, 1939
Donald B. Lindsley, 1937
Rafael Lorente de Nó, 1937
Horace W. Magoun, 1937
George L. Maison, 1939
Ade T. Milhorat, 1934
Hayden C. Nicholson, 1932
Seward E. Owen, 1938
Irving H. Page, 1937
Herbert Pollack, 1933
C. Ladd Prosser, 1935
Oscar W. Richards, 1934
Curt P. Richter, 1924
Francis O. Schmitt, 1930
Wilbur A. Selle, 1937
Herbert Shapiro, 1937
Herbert Silvette, 1933
Paul W. Smith, 1933
Franklin F. Snyder, 1936
Samuel Soskin, 1930
J. Newell Stannard, 1938
Isaac Starr, 1929
George W. Stavraky, 1937
Theodore J. B. Steir, 1938
Eugene U. Still, 1928
Maurice L. Tainter, 1929
George W. Thorn, 1939
George E. Wakerlin, 1933
C. Beecher Weld, 1936
Robert A. Woodbury, 1936
Clinton N. Woolsey, 1938
Leland C. Wyman, 1927
William B. Youmans, 1939

Recipients – 1989 APS and Section Awards

Ray G. Daggs Award

Bodil Schmidt-Nielsen, University of Florida

Orr E. Reynolds Award

David L. Crandall, American Cyanamid Company: "From Roxbury to Richmond: The Military Career of Henry P. Bowditch"

Charles D. Kochakian, University of Alabama at Birmingham, honorable mention: "The Role of Technology in the Delineation of the Anabolic Action of Testosterone"

Caroline tum Suden Professional Opportunities Awards

Douglas A. Bayliss, University of North Carolina
Donna L. Carden, Louisiana State University, Shreveport
Lin Gehua, University of Michigan
Diane J. Lu, Hospital for Sick Children, Toronto
Susan E. Mulroney, Georgetown University, Washington, DC
Bruce H. Swords, University of Alabama, Birmingham

1989 Caroline tum Suden Professional Opportunity Award Winners

NIDDK Minority Fellowship Awards

Della Bewernick-Montion, California State University
George T. Blevins, Jr., University of Arkansas
Cheryl Bliss, New York State College of Veterinary Medicine
Clivel G. Charlton, Meharry Medical College
Marina Chicurel, Brookline, Massachusetts
Claude Davis, Tuskegee University
Ruben Garcia, University of Puerto Rico
Michael E. Lozano, San Antonio, Texas
Blanca Ortiz, California State University, Los Angeles
Lorelei Ellazar Perez, Boston, Massachusetts
Marilys G. Randolph, Washington, DC
Gloria Jean Respress, New Orleans, Louisiana
Maria L. Ruiz, Brookline, Massachusetts
Priscilla Sanabria, University Central Caribe, Puerto Rico
Belay Tesfamariam, Boston University Medical Center
Cheryl Torrence-Campbell, Meharry Medical College
Alice R. Villalobos, University of Arizona

Procter & Gamble Professional Opportunities Awards

Cardiovascular Section

Daniel J. Cushing, East Carolina University
Ann Folta, University of Michigan
Patrick J. Pagano, New York Medical College
J. Keith Smith, Louisiana State University, Shreveport

Cell and General Physiology Section

Alexandra Kemendy, Emory University
Yoav Segal, University of Texas, Galveston

Endocrinology and Metabolism Section

S. Paul Rossby, University of Arkansas
Susan J. Vannucci, Pennsylvania State University

Environmental and Exercise Physiology Section

Ted S. Wong, University of Texas, Houston

Gastrointestinal Physiology Section

Laura Dunbar Lewis, University of Michigan

Nervous System Section

Mary I. Leadbetter, University of North Dakota

Neural Control and Autonomic Regulation Section

Julie Y. H. Chan, Washington State University
Christina Leone, Emory University

Renal Physiology Section

Nael A. McCarty, University of Texas, Houston

Respiratory Physiology Section

Bill T. Ameredes, Ohio State University
Karen A. Costa, St. John's University

Water and Electrolyte Homeostasis Section

Suzanne Greenberg, Medical College of Wisconsin

1989 Procter & Gamble Professional Opportunity Award Winners

APS and Section Awards

Society Awards

Caroline tum Suden Professional Opportunity Awards

The annual Caroline tum Suden Professional Opportunity Awards ($500, complimentary registration and placement service fees) are granted to as many as six male or female graduate students or postdoctoral fellows who present a contributed paper at the APS/FASEB Spring Meeting. Candidates must be the first author of an abstract submitted to APS. An accompanying letter, signed by the sponsor of the abstract, must contain *1*) certification that the author is a student or postdoctoral fellow and *2*) the approximate date the nominee will be available for employment. Awardees are notified by the Selection Committee prior to January 31, 1990 and presented with their awards during the APS Business Meeting.

NIDDK Travel Fellowships for Minority Physiologists

NIDDK Travel Fellowships for Minority Physiologists are open to advanced undergraduate, predoctoral, and postdoctoral scientists who have obtained their undergraduate education in Minority Biomedical Research Programs (MBRP) and MARC eligible institutions, as well as students in the APS Porter Development Program. Applications may also be submitted by minority faculty members at the above institutions. Funds will provide transportation, meals, and lodging to attend the annual APS/FASEB Spring Meeting in Washington, DC, April 1–5, 1990. The specific intent of this award is to increase participation of the pre- and postdoctoral minority students in physiological sciences. Applicants need not be members of the APS but should be a US citizen or hold a Permanent Resident visa. Applications should include *1*) information on academic background and experience; *2*) a written statement of interest in research in physiology; *3*) a letter of recommendation from the applicant's mentor; *4*) a list of publications, if available; *5*) a statement indicating the underrepresented minority (Black, Hispanic, or American Indian) with which the applicant identifies himself/herself; *6*) an estimate of required travel and per diem expenses. The deadline for receipt of completed applications is December 8, 1989. Awardees will be notified before January 31, 1990.

John F. Perkins, Jr. Memorial Fellowship

The American Physiological Society invites applications for the John F. Perkins, Jr. Memorial Fellowships. The Perkins Fellowships are designed primarily to provide supplementary support to foreign physiologists who have already arranged for fellowships or sabbatical leave to carry out scientific work in the United States.

The supplementary support is intended to help foreign scientists bring their families to the United States and thus enable them to take fullest advantage of the cultural benefits inherent in international exchange.

Preference will be given to physiologists working in the fields of respiratory physiology, neurophysiology, and temperature regulation. Applications from scientists in developing countries will also be given special attention.

Each application should be made by both visiting scientist and host. The application should contain an account of these arrangements with a brief description of the proposed scientific work and an account of how visitors and their families intend to make use of cultural opportunities during their stay. Deadlines for receipt of applications are June 1 and December 1. Applications may be obtained from the Executive Director, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814, USA.

Orr E. Reynolds Historical Award

The Orr E. Reynolds Award is given annually by the American Physiological Society for the best historical article submitted by a member of the Society.

Articles may deal with any aspect of the history of physiology including the development of physiological ideas and their application, instrumentation, individual and collective biography, departmental and institutional history, history of societies including APS, and physiology in its public context. Manuscripts submitted for the award should represent original research and be adequately documented. Articles published in APS journals or books during the prior calendar year are also eligible for the award upon request by the author(s). The award is open to all classes of APS membership except for those members who have advanced degrees in the history of science and medicine. A member may received the award only once.

The awardee will receive $500 plus expenses to attend the APS Spring Meeting. If the awardee wishes, and there is a suitable place on the program, an oral presentation will be made at the Spring or subsequent Fall meeting at the beginning of an appropriate scientific session. It is hoped that, after appropriate peer review, the article will be published in one of the APS journals.

Manuscripts will be evaluated by a committee consisting of three members of APS apointed annually by Council in consultation with the Chairman of the Section of the History of Physiology. At least one of the members will be a professinal historian.

Manuscripts should be typed and double-spaced with wide margins on 8½ × 11 paper and should conform to the style used in APS journals. (Instructions will be sent on request.) Three copies should be submitted for use of the review committee. To be considered for the 1990 award, manuscripts should be sent to Orr E. Reynolds Award, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814, by December 1, 1989. The recipient of the award will be announced at the 1990 Spring Meeting.

APS Membership Applications

Membership applications may be obtained from APS Membership Services, 9650 Rockville Pike, Bethesda, MD 20814. Applications received between February 1 and July 1 are considered for nomination by Council at the Fall Meeting, and those received between July 1 and February 1 are considered for nomination at the Spring Meeting of the Society.

(see p. 137)

Section Awards

Procter & Gamble Professional Opportunity Awards

The Procter & Gamble Professional Opportunity Awards (provides $500 and complimentary registration for the APS/FASEB Spring Meeting) are granted to at least 17 predoctoral students who present a contributed paper at the meeting. Candidates must be the first author of an abstract submitted to APS and within 12–18 months of completing his/her PhD degree. All recipients must be US citizens or hold a Permanent Resident visa. An accompanying letter, signed by the sponsor of the abstract, must contain *1*) certification that the author is a predoctoral student and *2*) the approximate date of degree completion. Awardees will be notified before February 15, 1990. Awardees are selected by the Sections of the APS. When submitting an abstract, please indicate (by appropriate number) which section should consider the abstract as indicated below:

1. Cardiovascular
2. Cell & General
3. Comparative
4. Endocrinology & Metabolism
5. Environmental & Exercise
6. Gastrointestinal
7. Nervous System
8. Neural Control & Autonomic Regulation
9. Renal
10. Respiratory
11. Teaching
12. Water & Electrolyte Homeostasis

Cardiovascular

The Cardiovascular Section presents three annual awards—Fellowship, the Lamport Award, and the Carl J. Wiggers Award. Nominations for **Fellowship Awards** must be made by at least two existing fellows with supporting letters sent to the steering committee for vote. The total number of fellows cannot exceed 5% of the APS regular members who have published meritorious research in cardiovascular physiology. The **Lamport Award** is presented to a young investigator under the age of 36 showing outstanding promise in his/her field of cardiovascular research. The recipient, who receives a certificate and a $200 check, is selected by the Wiggers awardee of the previous year. The **Carl J. Wiggers Award** honors a founder of the section and is presented to a scientist who has made outstanding and lasting contributions to cardiovascular research.

Cell and General Physiology

The Cell and General Physiology Section awards one undergraduate student ($200) and one postdoctoral student ($300) after three years of obtaining an MD or PhD degree.

Awards are made to students whose research in the field of cell physiology are judged to be an outstanding contribution. A recipient must *1*) be first author on an abstract submitted for the APS/FASEB Spring Meeting; *2*) perform research in the field of cell physiology; *3*) be a graduate or within three years of receiving his/her degree; and *4*) submit with his/her abstract a letter from the Department Chairman confirming his/her eligibilitiy. Recipients will be selected from those candidates who submit abstracts to Program Chairman of the APS Cell Section, Dr. Lazaro Mandel, Department of Physiology, Duke University Medical Center, Box 3709, Durham, NC 27710.

Comparative Physiology

The Comparative Physiology Section **Scholander Award** is presented annually to recognize an outstanding young investigator presenting a paper as first author in a comparative physiology slide session at the APS/FASEB Spring Meeting. Candidates must be graduate students or postdoctoral fellows, not more than five years beyond their highest degrees. The recipient receives a cash award of $100 and a certificate from the APS.

Environmental and Exercise Physiology

The Environmental and Exercise Physiology Section presents two annual rewards. The **Young Investigator Award** ($150) is for the recognition of excellence in research by a graduate student. The **Honor Award** ($200) is given to a member of the section who has had a lifetime of outstanding research. Candidates must be first author on a paper presented at a previous APS meeting. Honoring Harwood S. Beling, the awards are presented at the section dinner.

Gastrointestinal Physiology

The Gastrointestinal Physiology Section presents the **Smith Kline & French Young Investigators Awards** for outstanding pre- and postdoctoral research in gastrointestinal physiology. Two $300 awards are made at the APS/FASEB Spring Meeting. One is given for work done while enrolled as a student for a doctoral degree. A second award is given for work performed during the first through the third postdoctoral years. Applicant must be first author of an abstract submitted for the meeting. Abstracts accompanied by a sponsoring letter from the research advisor, stating the applicant is a graduate student or a postdoctoral fellow, should be sent to Dr. Joseph Fondacaro, Department of Pharmacology, Smith, Kline & French Labs, L520 P.O. Box 1539, King of Prussia, PA 19406, by December 15, 1989.

Nervous System

The **Van Harreveld Memorial Award** of the Nervous System Section is to honor the best APS student presentation at the APS/FASEB Spring Meeting. The award will be presented at the meeting.

Renal Physiology

The Renal Physiology Section **Award for Excellence in Renal Research** is to promote and develop excellence in research related to molecular, cellular, and organ mechanisms expressed by the kidneys. Annual awards are presented to a graduate and a postdoctoral student with judging based on abstract submission (25%) and meeting presentation (75%). Papers are evaluated by three judges in renal hemodynamics, epithelial transport, and metabolism. A certificate and prize of $200 are presented to the recipients at the annual renal dinner.

Deceased Members

Wright R. Adams, Gulf Shores, AL (09-04-88)
Walter M. Booker, Washington, DC (Sept. 1988)
Ko Kuei Chen, San Francisco, CA (Dec. 1988)
George H. A. Clowes, Dover, MA (09-10-88)
Julius J. Cohen, Rochester, NY (12-26-88)
Leonard A. Cohen, Detroit, MI (09-13-88)
Jefferson M. Crimson, Engelwood, CO (Nov. 1987)
Victor A. Drill, Glenview, IL (12-04-88)
Edward Eagle, Evanston, IL (09-28-88)
Frederick P. Ferguson, Bethesda, MD (09-20-88)
John W. Heim, Dayton, OH (Dec. 1988)
William T. McElroy, Jr., Shreveport, LA (11-03-88)
James R. Neely, Danfille, PA (11-29-88)
Jack Orloff, Bethesda, MD (12-06-88)
Albert E. Renold, Geneva, Switzerland (Spring 1988)
Paul Reznikoff, Madison, WI (Oct. 1988)
Louise Roquemore, Marshfield, MA (Oct. 1988)
Joseph E. Sokal, Durham, NC (Dec. 1988)
Klaus R. Unna, Chicago, IL (06-26-87)
Shizuo Watanabe, Chiba-Jen, Japan (July 1986)

Senior Physiologists News

Letters to John Brobeck

Bill Blake reports that his scientific career has ceased, but that he and his wife Rosemary are living a full life with lectures and concerts at Bowdin College, with their children and grandchildren who live in or near Brunswick, ME, and with other interests: traveling, gardening, and painting. The Blakes moved to Maine—where he has designed and built a house on Casco Bay—from Baltimore soon after his retirement in early 1979.

His wife, who started college in Baltimore, was accepted as a part-time student at Bowdin College and in 1986 was graduated Phi Beta Kappa and Summa cum Laude. Their travels have taken them to England four times (twice for five months), once to France, and once to China. They have stopped sailing but continue to garden. His painting has led to invitational group showings in London and North Carolina and a juried showing in Maine.

J. H. U. Brown writes that he was retired at the University of Houston as tenured faculty in June but will continue teaching on a year-to-year basis. He also notes that he is still active in research, having a grant from NASA to develop a patient medical records system for astronauts and a contract to develop a patient record system for several large delivery systems.

He also continued to actively publish and now has 30 books plus 3 more in some stage on the press. He also has been averaging about 16 papers a year, mostly on record systems and hardware, plus speaking engagements.

Letters to Roy O. Greep

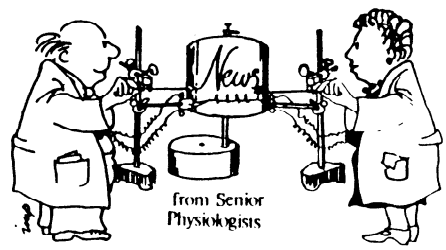
Seymour Katsh writes that he is at the University of Colorado Health Sciences Center in Denver where he is Physiology Professor Emeritus and Associate Dean Emeritus and where he acts in various capacities in other departments, including pharmacology, pathology, and ophthalmology. He also said that to pursue some exciting research projects he no longer consults for the university or outside agencies.

Robert S. Dow said when he retired in 1985, "Don't retire, just keep busy." That is what he is doing.

He and his wife Willetta spend almost every weekend at their second home on the eastern slope of Oregon's Cascade Mountains. But during the week in Portland he spends a half-day at the neurological clinic, where he has worked for 25 years before retiring, and is a part-time consultant at the Division of Clinical Neurophysiology at the Good Samaritan Hospital and Medical Center as well as being a consultant to the Good Samaritan Educational and Family Support Services.

In addition to winning several awards and collaborating on papers, he and Willetta are traveling, going to Europe twice and cruising the islands of the South Pacific and the Antarctica. The next trip is to Indonesia.

After his retirement from the University of Arkansas in May 1988 **John Sealander** has been busy revising his book on the mammals of Arkansas, which was first published in 1979 and will be republished in November of this year. A volume on Arkansas birds was published in 1987 and a volume on fishes of Arkansas was published last year. A volume on amphibians and reptiles is to follow within the next two years.



Letter to Steven Horvath

Edwin P. Hiatt says "I am emeritus in most of my academic interests but very lucky to feel good and fairly vigorous at age 77. My only scientific activity is as a part-time company physician for a Wilmington, OH, factory. There I look after the amazingly varied ailments of an essentially well population free from geriatric, pediatric, and obstetrical problems. What I make as a part-time physician enables me to continue farming. We raise beef feeder calves so most of our farm is in pasture and hay. My wife is very fond of golf so I have taken up the game after a hiatus of 50 years."

G. Edgar Folk, Jr. Senior Physiologists Fund

The G. Edgar Folk, Jr., Senior Physiologists Fund has been set up through the generosity of family and former graduate students and postdocs to provide modest but helpful assistance to senior physiologists 70 years or older who no longer have grant funds available to them. The awards might be used for such purposes as attending an APS meeting to present a paper, engaging in a series of modest experiments, or completing a manuscript (paying for typists or perhaps for page charges). Recipients will be selected with the assistance of the Senior Physiologists Committee throughout the year. Names of awardees will not be made public. Mary Folk writes that the purpose of the fund is for the Senior Physiologists Committee "to have *fun* assisting colleagues and for Emeritus APS members to keep in closer touch with APS."

Since the initiation of the program, 12 senior physiologists have received grants to pursue their research activities.

Inquiries concerning the G. Edgar Folk, Jr., Senior Physiologists Fund should be made to Martin Frank, Executive Director, APS.

Physiology and FASEB 1989

The 1989 FASEB Meeting in New Orleans was a joint meeting of five FASEB member societies and several guest societies. Over all, 6,694 abstracts of volunteered papers were submitted; 2,116 papers were submitted by APS members and two APS guest societies: the Society for Experimental Biology and Medicine (SEBM) and the Biomedical Engineering Society (BMES). The physiology component represented 32% of the short communications presented by APS members and guests.

Of the APS-sponsored papers, 19% (410) had women physiologists as first authors and 5% (110) were by members outside the Americas. In addition, 9% (206) were received from US Government laboratories and 3% (74) were received from physiologists employed by industry. Table 1 shows the departmental abstracts received by APS, of which 26% (545) were received from departments of physiology and 4% (98) were received from departments of physiology and biophysics.

Of the 2,116 APS-sponsored abstracts, 26% (552) were designated by authors for inclusion in topics programmed by other FASEB societies (Table 2).

Tables 3 and 4 show the distribution of programming of volunteered papers by Society sections. Of the 1,888 papers programmed by the Program Advisory Committee, 1,149 (61%) were scheduled for poster sessions, 592 (31%) for slide sessions, and 147 (8%) for poster-discussion sessions. Overall, there were 90 poster sessions, 54 slide sessions, 44 symposia sessions (including 5 debates, 1 workshop, and 1 tutorial), and 8 poster-discussion sessions. A total of 196 physiology sessions were scheduled.

TABLE 1. **Author Affiliations of Programmed Volunteered Papers**

Department	No. of Papers	% Total
Physiology	545	26
Physiology & biophysics	98	4
Medicine	212	10
Pharmacology	92	4
Biology	49	2
Surgery	71	3
Anesthesiology	82	3
Pediatrics	31	1
Biochemistry	21	1
Other	253	12

TABLE 2. **Volunteered Papers Sponsored by APS, SEBM, and BMES for FASEB '89**

Society	Total Received	FASEB Program Designation					
		APS	ASPET	AAP	AIN	AAI	Total
APS	1,983 (94%)	1,490 (70%)	230 (11%)	172 (8%)	73 (3%)	18 (1%)	1,983
SEBM	81	31	8	25	12	5	81
BMES	52	43	2	5	2	0	52
Total	2,116	1,564	240	202	87	23	2,116

TABLE 3. **APS Scientific Sessions at FASEB '89**

Section	Slide	Poster	Poster Discussion	Symposia*	Total
Cardiovascular	18	17		8	43
Cell & general	0	7		3	10
Comparative	1	4		1	6
Endocrinology & metabolism	7	13		0	20
Environmental & exercise	3	7		1	11
Epithelial	1	3		0	4
Gastrointestinal	1	6		4	11
History	0	1		1	2
Muscle	0	8		0	8
Nervous system	1	1		2	4
Neural control & autonomic regulation	4	5		0	9
Renal	5	4		2	11
Respiration	7	5	7	3	22
Teaching	0	0	1	1	2
Water & electrolyte	4	3		5	12
BMES	2	5		3	10
SEBM	0	0		1	1
Theme	0	1		8	9
Special (workshop)	0	0		1	1
Total	54	90	8	44	196

*Includes 5 debates and 1 tutorial.

TABLE 4. **Programming of Volunteered Papers by Sections/Groups**

Section	Slide	Poster	Poster Discussion	Total
Cardiovascular	215	313		528
Cell & general	0	66		66
Comparative	9	16		25
Endocrinology & metabolism	77	105		182
Environmental & exercise	27	96		123
Epithelial	13	69		82
Gastrointestinal	12	53		65
History	0	2		2
Muscle	0	76		76
Nervous system	8	33		41
Neural control & autonomic regulation	34	43		77
Renal	49	48		97
Respiration	82	144	138	364
Teaching	0	0	9	9
Water & electrolyte	45	47		92
BMES	21	31		52
Theme	0	7		7
Total	592	1,149	147	1,888

From Roxbury to Richmond: The Military Career of Henry P. Bowditch

David L. Crandall
Senior Research Scientist, American Cyanamid Company, Pearl River, New York

Introduction

When the American Physiological Society was established in December 1887, its first president, Dr. Henry P. Bowditch, entered into his new role with an established international reputation as a scientific investigator. Precisely 25 years earlier, however, Bowditch found himself in the uniform of a Union cavalry officer at the Battle of Fredericksburg, far from his studies at Harvard College. While Dr. Bowditch is reknowned today for his laboratory accomplishments in the field of physiology, little has been written about his military career. This is somewhat surprising, as Bowditch participated in many of the major battles of the eastern theater during the American Civil War. While Bowditch's personality was described by a student almost 30 years after the war as a man whose "carriage was suggestive of his military experiences," an in-depth examination of his wartime activities has yet to be performed. One must therefore wonder to what extent his abilities for training young men in the disciplines of scientific endeavor were influenced by his experiences in leading men into battle and to what degree his role in the Union cavalry contributed to his leadership traits.

Enlistment

In the spring of 1861, Henry P. Bowditch of West Roxbury was enrolled as a student at Harvard College, where he celebrated his 21st birthday on April 4. Two weeks later, gun batteries manned by militia of the recently declared independent state of South Carolina opened fire on government troops stationed at Ft. Sumter in Charleston harbor, and the War Between the States had begun. President Lincoln initially called for volunteers to enlist for a period of 90 days, and states began recruiting men to "smother the fire of rebellion." One great battle, First Manassas, was fought by the 90-day volunteers, the result of which was a realization by the Lincoln government that a major military effort would be required to defeat the Confederacy.

It was at this time, the autumn of 1861, that the 90-day volunteers were discharged and returned to their homes with tales of battle, while the threat posed by a large Confederate army camped across the Potomac River from the nation's capital remained in the minds of all who had served. One such soldier, Edwin Bennett of the 5th Massachusetts Volunteer Infantry, described the atmosphere in Boston in the fall of 1861: "Patriotism had now become a passion with the young men of the North. Those who had served three months were mastered by it. Nearly all found that they could not be content at home, while the fate of the country was at stake upon the field of battle." Henry Pickering Bowditch was one of the young men of whom Bennett spoke. Patriotism was not an unfamiliar ideal to young Bowditch. He was a direct descendant of Col. Timothy Pickering, General George Washington's Chief of Staff during the American Revolution, later to be named President Washington's Secretary of State. When War Department Special Order No. 419, dated September 3, 1861, authorized the raising of squadrons of cavalry to be organized into the 1st Regiment Massachusetts Volunteer Cavalry, Henry Bowditch was among those who heeded the call. Official documents record the enlistment as follows: Henry P. Bowditch, Jamaica Plain, student, age 21, was commissioned 2nd Lieutenant, 1st Massachusetts Volunteer Cavalry on November 5, 1861. The regiment was to consist of 1,200 men organized into 12 companies, 3 battalions, to be trained and outfitted for battle at Camp Brigham, Readville, Massachusetts. The men reported for duty throughout the autumn of 1861, which was unseasonably cold and damp. "Boot camp" consisted of mounted drill, complicated considerably by the fact that saddles were not made available until one week before the completion of training. While the conditions were discomforting, the sense of duty was aroused by occasional regimental parades through the streets of Boston and the constant anticipation of movement toward Richmond.

The Trip South

When Lt. Bowditch was mustered for duty, he was initially assigned to Company G, 2nd Battalion, 1st Massachusetts Volunteer Cavalry, which left Boston for the "seat of war" soon after Christmas Day, 1861. He had enlisted for 3 years and was accompanied by members of Boston's finest families, including his cousin Nathaniel Bowditch, son of a prominent Boston physician, and Charles Francis Adams, Jr., grandson of former President John Quincy Adams. The first leg of the journey south was by train to New York City, where his battalion's mounts were housed in the "excessively dirty and dilapidated" quarters of the Third Avenue Horse-Car

Company. The men were not treated much better, being quartered in an adjacent beer garden, where they celebrated New Year's Day 1862. On January 8, Bowditch's battalion received orders to board naval transports bound for Port Royal, South Carolina, in the vicinity of Charleston harbor. When the transports departed New York on Saturday, January 10, the weather had turned stormy, causing the ships to roll badly, producing havoc for the hundreds of horses housed in the vessels' holds. The torment was compounded by an outbreak of measles, which spread rapidly throughout the regiment. The suffering did not desist on arrival off the South Carolina coast some 10 days later, as Bowditch's vessel became grounded a good distance offshore. Thousands of dollars in equipment was thrown overboard to facilitate floating the great vessel free from harm's way and at the additional cost of spending several more days crammed into the measle-ridden ship's quarters.

When they finally disembarked, Bowditch's command was assigned to duty at Beaufort, South Carolina, with his regiment attached to the 15,000-man Southern Expeditionary Corps. The purpose of this force was to threaten Charleston, considered by many Northerners as the seat of rebellious Confederate thinking. The Corps did very little "soldiering," however, and instead spent their days either drilling for battle or ransacking the plantation homes of those rich Southerners who once inhabited the islands. On February 19, 1862, Bowditch's Company G was transferred to Edisto Island, a few miles from regimental headquarters in Beaufort. Early in May, a military plan was conceived to march the little army toward Charleston, which culminated on June 15 with the Union assault on the Confederate fort at Seccessionville. The battle involved a frontal assault against a well-fortified Confederate position, the disastrous result being 500 Union casualties and an inglorious retreat. Bowditch's regiment remained as a reserve unit during the battle, which was a common tactical maneuver for cavalry units during the early stages of the war. This was, however, the first hostile engagement encountered by the young lieutenant.

The 1st Massachusetts Volunteer Cavalry remained in South Carolina the better part of the summer of 1862, with no other significant engagements. The enemy in South Carolina now became the weather, the insects, and the bad food, which eventually contributed to an epidemic of "black bilious fever." In fact, regimental records indicate that several officers, including Bowditch's cousin Nathaniel, were allowed to return to Boston on sick leave that summer. At last, on August 19, 1862, the campaign in South Carolina ended, with orders issued for the troops to be transported to Virginia. The regiment now became officially attached to the Army of the Potomac, where it would be ordered against the Confederate army of General Robert E. Lee. Interestingly, Henry Bowditch, recently promoted to 1st Lieutenant of Company E, remained in South Carolina in charge of remnants of eight separate companies, a total of 80 men who could not "get transportation." He remained on duty assigned to maintain the Union control of the South Carolina waterways but was at no time seriously threatened by hostile forces.

A rare photo of Henry P. Bowditch taken by the famous Civil War photographer Mathew Brady. Bowditch is in the uniform of a 2nd Lieutenant, and the emblem on his hat indicates his membership in the 1st Massachusetts Volunteer Cavalry. Brady maintained studios in both New York and Washington, DC, but because of his rank, this photo was probably taken of Bowditch during his trip through New York on his way to South Carolina. (Reproduced from the regimental history.)

Meanwhile, the 1st and 2nd Battalions of his regiment, including his cousin Nathaniel, were engaged repeatedly throughout the month of September, culminating in their participation in the Battle of Antietam, the war's "bloodiest day." Early in November, Bowditch was reunited with his command in Washington, DC, where he was ordered to report to Major Henry Higginson. It must have been at this juncture in the war where Higginson quoted Bowditch as expressing his distaste for the army life. The encounter was recreated by a medical student of Bowditch's some 75 years later as follows: "In a conversation with Major Higginson, after the Battle of Antietam, Bowditch confessed that he had no liking for Army life, and that he longed for the time when he could devote himself to scientific studies." While only speculation can recreate Bowditch's reasoning behind this statement, perhaps he was disappointed to be ordered to re-

main behind in South Carolina while the bulk of his regiment fought Lee in Virginia. Possibly, too, he was simply fatigued by the irrepressible personal discomfort he had experienced since reporting to Camp Brigham some 10 months earlier. Regardless, Bowditch was not at the Battle of Antietam, as the statement implies, and had seen almost nothing of the carnage of war. As his military record indicates, however, he was about to embark on the road to becoming a battle-hardened veteran tested repeatedly by enemy fire.

1863 – The Metamorphosis of the Union Cavalry

Bowditch traveled from Washington, DC to regimental headquarters in northern Virginia where, in December 1862, he was again held in reserve during the Battle of Fredericksburg. While this was a major battle of the Civil War, it was fought primarily by infantry and artillery units, with mounted soldiers having very little active participation. The Union commander, General Ambrose Burnside, failed hopelessly in assaulting the Confederate positions on Marye's Heights, resulting in an incredible loss of human life and his inevitable dismissal as commander of the Army of the Potomac. While his replacement, General Joseph Hooker, would not prove much better in battle, he held the belief that the cavalry should take a more active combative role in the war. During the winter of 1862–1863, the restructuring of the Union cavalry therefore began, and Bowditch's regiment was soon to undergo an organizational metamorphosis. Under Hooker, the cavalry would no longer be used simply for escort purposes or reconnaissance but would be committed in battle as an independent fighting unit.

To prove their ability to match the Confederate horsemen of J. E. B. Stuart, Hooker ordered 3,000 Union troopers against the rebels in mid-March 1863, the purpose being to "rout and destroy the enemy." A brigade of Virginia cavalry led by Fitzhugh Lee, nephew of the Confederate commander, was known to be in the vicinity of Culpeper, Virginia, across the Rappahannock River from the Federal camps. At 4:00 A.M. on the morning of March 17, St. Patrick's Day of 1863, the Union troopers were organized along the northern bank of the river. Three members of the 1st Massachusetts were detached as staff officers of the different brigade commanders, among them being Nathaniel Bowditch, who was assigned as an adjutant to Duffié's brigade. The remainder of the 1st Massachusetts remained intact.

At 8:00 A.M., the Union forces began crossing the river at Kelly's Ford but met considerable resistance in the form of rebel sharpshooters positioned along the opposite bank. Duffié's brigade had crossed by noon, where, with the rest of the force now numbering about 2,000, they prepared for battle. Fitzhugh Lee's Confederates immediately attacked on horseback, but the Union troopers waited until the enemy was within 100 yards of their line before countercharging. Lieutenant Nathaniel Bowditch actively led the Federal charge and, with sabre drawn, was engaged in hand to hand combat with the enemy. Regimental history records the events as follows:

> Lieutenant Bowditch greatly distinguished himself in this charge, knocking out of their saddles three Confederates. His horse was killed, and he received three wounds. When lying on the ground helpless he was shot through the bowels, and mortally wounded, dying in the camp the next day, much regretted by everybody in the brigade. He was a gallant and genial officer.

The Battle of Kelly's Ford continued until around 5:00 P.M., when the Union commander, fearing rebel reinforcements, withdrew his troops back across the river. Nathaniel Bowditch remained on the battlefield where, despite his serious abdominal wound, he was never approached by medical personnel. His injury was complicated when he was finally removed on horseback instead of being transported by ambulance.

While the battle raged for almost nine hours, Henry Bowditch was riding with the bulk of the regiment toward Warrenton, where a large force of enemy cavalry was supposedly sighted. The enemy never materialized, and with the exception of the three detached staff officers, the 1st Massachusetts did not participate in the first major battle of the Civil War that was fought entirely on horseback. Initial

Another photo of Bowditch in the uniform of a 2nd Lieutenant, obtained from a collection previously housed in the Boston Armory. Because Bowditch was promoted to 1st Lieutenant within several months of his enlistment, this photo was probably taken in Boston immediately before his departure for South Carolina. (From the US Military History Institute.)

reports from the battlefield had listed Henry, not Nathaniel, as mortally wounded, and were corrected on the official casualty list. It is of note that the death of Nathaniel so grieved his father, Dr. Henry I. Bowditch of Boston, that he began a national campaign for reform of the Ambulance Corps. In fact, he was largely credited with implementing practices in wartime medicine that remain today. As for Henry, he had now personally experienced the tragedy so typical of this war.

The results at Kelly's Ford, while not outright victory, stimulated the Union cavalry to continue offensive actions against the Confederacy, and Henry Bowditch, now promoted to Captain of Company E, was actively engaged throughout 1863. He participated in the "Stoneman Raid" the latter part of April and was in the near vicinity of Chancellorsville during the battle that took Stonewall Jackson's life. During May, a cavalry bureau was established in Washington, and General Alfred Pleasonton was appointed field commander of the corps. Spring was always a good time to begin campaigning, as the horses and men had been rested and provided new equipment during winter quartering. This spring, intelligence reports indicated that Lee was planning an invasion of the North, in preparation for which he was concentrating his cavalry in the vicinity of Culpeper County, Virginia.

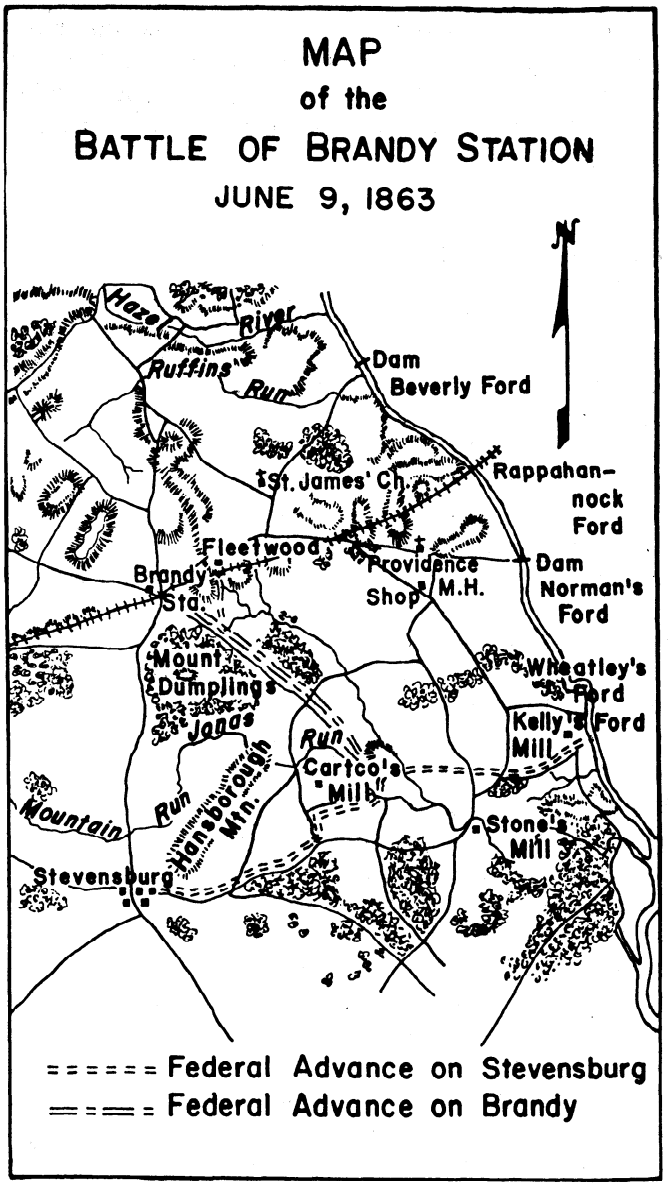
On June 8, around 2:00 P.M., a Union cavalry force of approximately 10,000 men departed Warrenton bound for the banks of the Rappahannock River, where an unsuspecting rebel force of equal number was camped. Bowditch's 1st Massachusetts was again assigned to the brigade of Colonel Duffié, who due to some confusion in interpreting his orders did not arrive opposite the Confederate camps until sometime after midnight. After only 2 hours of sleep, the weary troopers were awakened and ordered to Brandy Station via Stevensburg, while the main force marched directly to Brandy Station. The Battle of Brandy Station, considered the major cavalry battle of the Civil War, was fought on June 9, 1863 by a combined force of about 20,000 Union and Confederate cavalrymen. Bowditch's Company E was involved in heavy fighting approximately 4 miles from Brandy Station, in the vicinity of Stevensburg. According to regimental history, his company led a charge against men of the 2nd South Carolina and 4th Virginia cavalry, resulting in the capture of 53 prisoners and the killing of the Confederate commander. The rebels then retreated toward their forces located at Brandy Station, pursued by Duffié's brigade, which reached the main site of battle too late to take part in the most active fighting. In the late afternoon, Pleasonton, correctly believing that Confederate infantry were arriving as reinforcements, ordered his Union cavalry to retreat to safety across the Rappahannock. Casualty lists for each side indicated approximately 500 Confederate and 1,000 Union troopers as either killed, wounded, or missing. Bowditch had participated in the flanking movement of the battle and was present during what historians have claimed was the engagement that "made the Union cavalry." This battle had involved men of great military prowess, including George Armstrong Custer of the Union and J. E. B. Stuart of the Confederacy. Both sides agreed that the importance of the outcome was the confidence gained by the Union horsemen, who had at last held their own against what had previously been the superior Southern trooper. The days of escorting instead of fighting were erased forever.

The Battle of Aldie: "A Fight of Veterans"

In mid-June 1863, Lee's invasion of the North began in earnest. To prevent the Federal army from detecting the Confederate march northward along the Shenandoah Valley, Lee placed his cavalry east of the mountains in the vicinity of Aldie, Virginia. The Union generals, suspicious of Lee's plans, ordered Pleasonton's cavalry corps toward Aldie in an attempt to gather information on rebel troop movements. At 3:00 A.M. on June 17, the corps, now numbering approximately 7,000 troopers, was ordered to march from Manassas Junction to Aldie and to "scout the country well in the vicinity." Most of the regiments, Bowditch's included, now numbered only about 300 men, as the toll of the battles of 1863 were becoming evident. This decrease in the number of active troops again forced the reorganization of the corps, with the 1st Massachusetts being assigned to Kilpatrick's brigade of Gregg's Second Division. Around noon on the 17th, the vanguard of the corps, led by the 1st Massachusetts itself, reached Aldie and immediately encountered the Confederate cavalry of Fitzhugh Lee. The terrain of the battlefield favored the defensive positions the Confederates held behind stone fences, across ditches, and on hills. While also outnumbered, Kilpatrick ordered the 1st Massachusetts to charge the enemy on horseback, and the Battle of Aldie had begun. The regiment was composed of eight companies at the time, with Bowditch's Company E attached to the second squadron. The battle consisted of a series of charges and countercharges, hand-to-hand fighting with sabres, and carbine and pistol fire at close range. At one point in the battle, the regiment led a charge along a turnpike bordered by a deep ditch, behind which the Confederates had posted concealed sharpshooters. As the unknowing troopers galloped forward, they were ambushed by the rebels, resulting in an incredible loss of human life. The action was described by the Confederate commander as follows:

> As the enemy came up again, the sharpshooters opened fire upon him with terrible effect from the stone wall, which they had regained, and checked him completely. I do not hesitate to say that I have never seen as many Yankees killed in the same space of ground in any fight I have ever seen, or on any battlefield in Virginia that I have ever been over.

Seeing the plight of the Massachusetts troopers, Kilpatrick ordered reinforcements forward, who immediately rushed on the rebel sharpshooters, capturing the entire group. This aid was too late for many in Bowditch's regiment, however, as of the 298 members who rode into Aldie that afternoon, 167 were listed as casualties when the fighting ceased that evening. Many of the men had died in the rebel ambush, some of whom were killed even after surrendering. That day, the 1st Massachusetts had sustained an incredible 55% casualty



A map of the Battle of Brandy Station, also indicating the location of Kelly's Ford and Stevensburg. Present-day maps show this vicinity as approximately 45 miles southwest of Washington, DC and 25 miles due west of Fredericksburg, Virginia. (Reproduced with permission from the Louisiana State University Press.)

rate, and of the 1,200 original member strength that departed Boston at Christmastime 1861, only about 12% were available for duty as night fell on Aldie. Regimental history records this battle as the pinnacle of the war, as at no other time did so many well-trained veterans enter into battle under the regimental guidon. It was truly a "fight of veterans." Captain Henry P. Bowditch had seen considerable action, and a number of his company members were casualties at Aldie. In one skirmish, his company color-bearer was wounded, and although the flag was struck six times by enemy fire, it was heroically saved from capture by another member of the regiment. Picket duty in South Carolina must have seemed a distant memory that evening over 125 years ago; yet the regiment could not rest for long, as Lee continued to march toward Gettysburg.

Summer 1863: From Gettysburg to Bristoe Station

After Aldie, the 1st Massachusetts was so depleted that it could no longer function as a viable combat unit, yet it remained on active duty. During the Battle of Gettysburg a fortnight later, Bowditch, soon to be promoted to squadron commander, was present but not deployed for battle. Instead, his regiment served provost and escort duty during the second and third day of Gettysburg, July 2–3, 1863. The battle itself involved approximately 75,000 Confederate and 82,000 Union troops, with over 50,000 casualties in terms of killed, wounded, or missing. Bowditch certainly must have witnessed the horrifying results of the conflict. The Battle of Gettysburg was considered the "high tide of the Confederacy," a defeat for Lee, and a turning point in the war. To that end, the remainder of the summer on into autumn, the regiment, now reinforced, pursued Lee into northern Virginia. It was "a time of severe marching, but little fighting," as the two great armies maneuvered to gain a strategic advantage. They did remain in close contact, however, and skirmishes were fought by Bowditch's men at Jones Cross Roads on July 11, Culpeper on September 13, and Rapidan Station on September 14. In each of these, J. E. B. Stuart's cavalry was the foe, the same opposition Bowditch had faced continually throughout that year. In mid-October 1863, the regiment was engaged at the Battle of Bristoe Station, which involved a night attack by Stuart that forced a retreat by the Union army to Centreville, Virginia. The cold winds that had always signaled the end of the year's campaigning now found each army in defensive positions of strength, as soldiers from both sides prepared for winter quarters after what they expected was the end to the bloodiest year the country had ever witnessed.

The Mine Run Campaign: Bowditch Wounded and Missing in Action

To the dismay of the Army of the Potomac, the Lincoln government urged a final offensive against Lee on November 26, 1863. This expedition was to attack the Confederates northwest of Richmond in the vicinity of the Wilderness, along the Mine Run. On Thanksgiving Day 1863, the 2nd Cavalry Division spent the night, remembered as a very cold one, in the vicinity of Spotsylvania Court House. The next morning, now joined by General Meade's 5th Infantry Corps, the 1st Massachusetts led the expedition into the Wilderness, an area of thick and impenetrable woods. The Confederates were first encountered at New Hope Church where, because they were in the van, Bowditch's regiment was immediately fired upon. General Gregg himself rode to the front of the column, specifically ordering Bowditch to dismount his men along the side of the road. Once dismounted, they advanced through the dense woods, driving the enemy before them. At one point in the battle, Bowditch was shot through the arm while leading a charge, yet his men fought on, eventually taking a number of prisoners. These captives were members of General Wade Hampton's and A. P. Hill's Corps, both reknowned Confederate leaders.

In an official dispatch dated December 4, 1863, General Gregg described the Battle of New Hope Church as follows:

> On the morning of the 27th, pursuant to orders from the major-general commanding Cavalry Corps, the division moved to Parker's Store, passing on to Orange plank road in advance of the Fifth Army Corps. At New Hope Meeting House the First Brigade, Col. J. P. Taylor commanding, met the pickets and first line of skirmishers of the enemy's cavalry. Two squadrons of the Third Pennsylvania Cavalry and one of the First Massachusetts Cavalry, dismounted, drove back this line. The enemy endeavored to check the advance by discharges of cannister and shell from a piece of artillery, but uselessly. A section of Martin's (Sixth New York) battery placed at the meeting house compelled the withdrawal of this piece. Additional squadrons of dismounted men were now moved upon the skirmish line, and the enemy rapidly driven a mile beyond the meeting house. At this point the enemy's cavalry disappeared behind a line of infantry, which advanced to meet the line of the division; a battery of artillery opened from the enemy's right. To check this advance, four regiments, the Third Pennsylvania, First Massachusetts, First Pennsylvania, and First New Jersey, were dismounted and moved to the front, and two sections of Martin's battery placed in position close upon our line. This strong line of dismounted cavalry rushed upon the enemy, firing volleys from their carbines, and drove the infantry line to the cover of a dense woods and there held it at bay. Thirty-four prisoners were brought out and reported themselves as belonging to Hill's corps.
>
> Major-General Sykes, having joined me at this time, moved forward one of this divisions, and late in the evening my division retired within his lines. In this action, the regiments and battery of the 1st Brigade behaved most handsomely.

The wound Bowditch had sustained in the fighting forced him to the rear of the army, but his whereabouts remained unknown to the high command in Washington. In an official War Department communique telegraphed on December 5, the Adjutant General's office requested the following information from the Army of the Potomac: "Please inform this office by telegraph whether Capt. Henry P. Bowditch 1st Mass Cavalry is wounded & if so how badly—Also where is he now." The response, currently in the National Archives, came quickly:

> December 5, 1863, 6:45 P.M., Headquarters, Army of the Potomac
>
> Captain Henry P. Bowditch 1st Mass. Cavalry was wounded in the arm but not seriously on the 27th ultimo, and was sent to Washington where he is now supposed to be. A telegram was sent to his father at Boston informing him that the wound was not a dangerous one.

On December 1, the regiment went into winter quarters at Warrenton, Virginia, as Captain Bowditch made his way homeward. He was examined in Boston on January 15, 1864, where the surgeon reported that "he is invalided in Boston in consequence of a gun shot wound received in the late advance over the Rapidan." He was found unfit for duty for at least 20 days dated as of January 17. On the third of February he was reexamined by the same surgeon, who stated that "he is invalided in Boston suffering from a gunshot wound in right arm received at Mine Run Nov. 27, 1863. The wound is still suppurating." On February 15, 1864, Captain Henry P. Bowditch was honorably discharged as a result of his wound. He had fought with the Army of the Potomac throughout the campaigns of 1863, ending with a wound sustained during a charge led on foot against the enemy. He had served his country well, and if he so desired, could at last return to his studies in Boston.

Henry Bowditch in the uniform of Major, United States Volunteers. A comparison of the photos in this series reveals the aging effects of war, even though Bowditch was only 24 years old when commissioned to the rank of major. (From the US Military History Institute.)

Reenlistment in the Fifth Massachusetts: On to Richmond

In the spring of 1864, a new battalion was recruited to replace the casualties sustained by the 1st Massachusetts Cavalry to that point in the war. The method of staffing this battalion was to assign new, untested officers who had seen nothing of battle, instead of granting commissions and promotions to those currently in the existing ranks. This unfair procedure greatly demoralized the regiment, not only because of the absence of well-deserved promotions, but because veterans would be required to fight alongside, and rely on, comrades who had yet to be tested by enemy fire. The implication is made, and Henry Bowditch's name is specifically mentioned, as one of those seasoned officers who should have received a promotion into the new battalion in March 1864. He most certainly was seeking another military post after his medical discharge, because on March 26, 1864, he was commissioned as Major in the Fifth Regiment Massachusetts Volunteer Cavalry. This newly formed regiment was

the only Massachusetts cavalry regiment composed exclusively of blacks and was led by white officers who had distinguished themselves in earlier campaigns. Importantly, this regiment served as a dismounted unit, even though technically designated as cavalry. Later that spring, the Fifth Massachusetts departed Boston for northern Virginia, where on May 16 it was assigned to General Hinks Division of Smith's Corps.

During the spring of 1864, General Grant, now commanding the Army of the Potomac, attempted to capture Richmond through a brilliant flanking maneuver south and east of the city in the vicinity of Petersburg. The movement was undetected by Beauregard's Confederate troops, and accordingly Grant ordered his Union army to attack with the hopes of finally ending the war. On June 15, 1864, precisely 4 months after he had received an honorable discharge for wounds sustained in battle, Bowditch was actively participating in the advance on Petersburg, where his regiment was met by the enemy at Baylor's Farm. The unit was anxious enough to experience their first real combat but not well-trained or equipped. During the fighting that ensued, the regimental commander was seriously wounded, and command passed to Major Bowditch. At 7:00 P.M. that evening, approximately 3,700 Union troops participated in a frontal assault against the Petersburg defenses, successfully driving the rebels toward Richmond and capturing five confederate redans that guarded the city. Bowditch's regiment represented one-quarter of the Union troops actively involved in the fighting, and his valor and that of his regiment had resulted in the successful opening of a mile-wide gap in the Confederate fortifications. Petersburg, as well as Richmond, lay open to the Union army. As had occurred innumerable times in the past, however, the Union generals were hesitant to attack further, thereby allowing time for the Confederates to reinforce their defensive works.

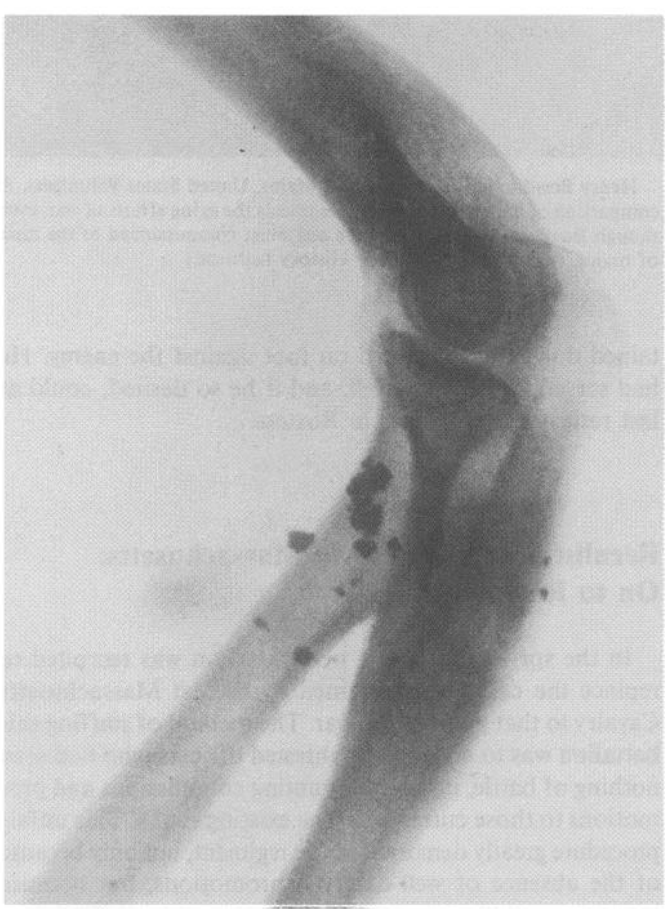
The fighting that day was described in the following official report:

> HDQ. Third Division, 18th Army Corp, In the Field, Virginia, June 27, 1864
>
> To: Major General W. F. Smith, Commanding 18th Army Corps
>
> In forming line of battle in the morning, for the attack upon the enemy's works near Baylor's house, I placed the 5th Mass. Cav. (dismounted) on the left of the 2nd line of battle, and its awkwardness in maneuvering delayed my movement fully three-quarters of an hour, and finally when it advanced, though nobly and heroically led, it was but little other than an armed mob, which was held up to its work by the almost superhuman efforts of its officers. Its losses were heavy, among them being its gallant commander (Colonel Russell) and Major Adams, while its power to inflict injury upon the enemy was nominal. I could but commend its gallantry, but considering its inefficiency, decided that to further engage it with the enemy would be a reckless and useless expense of life to no purpose.
>
> General E. W. Hinks, Brig. General,
> U.S. Volunteers.

In retrospect, historians blamed the Union high command, not the Massachusetts regiment, for the failures of June 15. Bowditch's heroism had been wasted, and the siege of Petersburg had begun.

After the Battle of Baylor's Farm, the regiment remained in the vicinity of Richmond, during which time General Hinks wrote several more communiques concerning its questionable fitness for battle. The most often mentioned concern was the fact that the unit was trained in cavalry tactics yet was being committed as an infantry unit. At last, on June 21 the regiment was ordered to Point Lookout, Maryland to guard Confederate prisoners of war. Here it remained throughout 1864, while its officers, including Major Bowditch, performed duty in military courts. This also allowed additional time for training and drill, as well as the procurement of horses for the 900 members of the regiment.

In March of 1865, the Fifth Regiment, now properly mounted and trained, was ordered to return to the fighting in front of Richmond as part of Weitzel's command. During the night and early morning hours of April 2–3, 1865, the President of the Confederacy, Jefferson Davis, as well as his cabinet and staff, left the capital under the cover of darkness. Riots and vandalism by the citizens and soldiers that re-



The X-ray of Bowditch's right arm clearly revealing the fragments of the Confederate bullet that wounded him at the Battle of New Hope Church during the Mine Run Campaign in November 1863. This X-ray was taken in 1896 in the physiology laboratories of Harvard Medical School. According to Michael J. Winey, Curator at the US Military History Institute, even by late 1863 Confederate soldiers used whatever shoulder arms they could obtain. The most often used rifle calibers were .54, .577, .58, and .69, but with pistols and muskets also being prevalent, calibers ranged from .22 to .80, with almost every interval between being covered. Mr. Winey could not determine from the fragments in Henry Bowditch's arm which caliber of bullet caused his wound. (Provided by Dr. A. Clifford Barger.)

mained soon followed, and the entire business district of Richmond was set afire. The Union troops were close enough to observe the smoke and flames erupting from the city, and at first light, suspecting that the city was vulnerable, General Weitzel ordered his cavalry forward on reconnaissance. Bowditch and the Fifth Massachusetts were among those sent into Richmond that morning, which, unknown to them, had now been completely abandoned by the Confederate army. By an incredible set of circumstances, Henry Bowditch was one of the first Union officers to enter the fallen Confederate capital, the prize the Army of the Potomac had sought for four bloody years. The following day he would celebrate his 25th birthday. Charles Francis Adams, Jr., now at the head of the regiment, described his feelings in a letter to his father, the ambassador to England: "To have led my regiment into Richmond at the moment of its capture is the one event which I would most have desired as the culmination of my life in the army." This, too, was to be the culmination of Bowditch's military career, for after being assigned to patrolling the nearby vicinity for a month, he resigned his commission and was honorably discharged on June 3, 1865. Lee had surrendered at Appomattox Court House, and the need for the use of force no longer existed. For Major Bowditch, as for many, the war was over.

Return to Boston: The Final Chapter

Henry P. Bowditch's military career had been a distinguished one, about which surprisingly little has been written. The most often quoted description of Bowditch as a Union officer is that of Henry Lee Higginson, a major in the 1st Massachusetts Cavalry. In Cannon's obituary of Bowditch, he quotes Higginson as describing Bowditch during the war as "a handsome, refined, and homebred youth, with a fondness and faculty for keeping face clean and clothing neat when those attributes were a rarity." He continued by saying that Bowditch was "an upright and fine officer, often reserved and even unbending in his manner, but unflagging in his faithfulness and unfliching in his courage." Interestingly, Higginson was severly wounded at Aldie and never again returned to active duty after mid-June 1863. His descriptions of Bowditch, while complimentary, must therefore predate many of Bowditch's military experiences. Importantly, Bowditch continued his command development after Higginson's acquaintance, becoming a squadron leader in July 1863, being wounded while leading a charge in November, and ending his military career as a battalion commander with the rank of Major of U.S. Volunteers. He had shown the loyalty to his country that had typified his heritage and could now return to Boston a hero in his own right.

Bowditch's life after the Civil War is extremely well documented. After his return to Boston, he graduated from Harvard Medical School, receiving an M.A. in 1866 and M.D. degree in 1868. He then traveled abroad for three years, furthering his education in several European institutions. On returning home in 1871, he took a position on the Harvard faculty, eventually being appointed dean of the medical school. His role as founder of the American Physiological Society and as a pioneer in medical education and research brought him the fame for which he is remembered. Interestingly, during this period a final chapter was written in Bowditch's Civil War career. In 1895, the German physicist Wilhelm Roentgen had discovered X-rays, and in late 1896 this

1989 Orr E. Reynolds Award

The Orr E. Reynolds Award is given in honor of our second Executive Secretary-Treasurer and is presented for the best historical article submitted by a member of our Society. The first winner of this award was John B. West in 1987. This year's recipient is **David L. Crandall,** Senior Research Scientist, Cardiovascular Research Department, American Cyanamid Company.

In receiving the award at the 1989 APS Spring Business Meeting, Dr. Crandall said, "I am thrilled to have won this distinguished award and thank the selection committee. I want to especially express my appreciation to Clifford Barger, who went to the Harvard archives and provided me with rare archival material. Without his assistance the article could not have been written. I hope you enjoy reading it. Thank you."

Charles D. Kochakian, from the University of Alabama at Birmingham, received an honorary mention for his article entitled, "The Role of Technology in the Delineation of the Anabolic Action of Testosterone."

David L. Crandall and APS President Aubrey E. Taylor

technology was first brought to the Harvard Medical School by Dr. Ernest Amory Codman. The apparatus was assembled in the Anatomy Department of the Medical School building at the corner of Boylston and Exeter Streets, and Dr. Bowditch volunteered to have his right arm subjected to these "invisible" rays. In one of the first radiological examinations done in the United States, the fragments of the Confederate bullet that Bowditch had carried since the Battle of New Hope Church were revealed. This image, developed by Codman, hung in the Physiology Department of the Harvard Medical School for some 75 years. To this point in time, it has served as a tribute to Bowditch's military career and contributions to science. It also, however, stimulated Bowditch to suggest to Walter B. Cannon that X-rays be used as a research tool for investigation in physiology. Cannon, then a student at Harvard, immediately employed Codman's novel instrument to study the mechanism of gastric motility, the results of which he presented at the American Physiology Society meeting in December 1896 and published in the first issue of the *American Journal of Physiology* in January 1898. Bowditch's wound had, in a very direct way, contributed to initial investigations that would have profound effects on the fields of radiology, gasteroenterology, and gasterointestinal physiology. The history of these specialties of medical science were integrally linked to Henry Bowditch's remarkable military career, which had begun with his enlistment in Roxbury and culminated with the capture of Richmond.

I would like to express my gratitude to Majors Robert Dunn and Daniel Drummond, United States Army; Holbrook W. Yorke, United States Military Academy Library; Katherine Griffin, Massachusetts Historical Society Library; Randy Hackenburg, United States Military History Institute; A. Clifford Barger, Harvard Medical School; and photographers Jim Enos and John Vallancourt.

Suggested Readings

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3. Starr, S. Z. *The Union Cavalry in the Civil War.* Published by the Louisiana State University Press, 1979, vol. 1–3.
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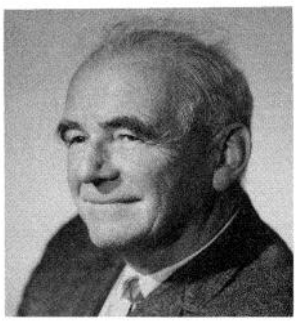
Dedication of Scholander Hall



The Physiological Research Laboratory at the Scripps Institution of Oceanography, University of California–San Diego, has been renamed Scholander Hall to honor the contributions made by Professor Per F. (Pete) Scholander in physiology and medicine. Scholander, the first director of the Physiological Research Laboratory, made seminal contributions to such diverse areas as diving physiology of marine mammals, thermal regulation in mammals from different latitudes, the transport of solutes in vascular plants, and osmotic theory. His clever development of unique instrumentation, notably for measuring small volumes of gasses and osmotic phenomena, complemented his theoretical achievements. Scholander conceived the idea for a sophisticated sea-going research laboratory devoted to experimental biology. His dream became a reality with the launching of the Research Vessel Alpha Helix in 1966. The Physiological Research Laboratory, also a creation of Scholander, was built on the Scripps campus as a complement to the Alpha Helix.

Scholander's long, innovative, and wide-ranging career in science is discussed in his forthcoming autobiography, *Enjoying A Life in Science,* which will be published later this year by the University of Alaska Press.

APS member **Michael J. Dimino,** PhD, Eastern Virginia Medical School, has accepted a position at the University of Alaska, Anchorage, WAMI Program.

Formerly at the Kuwait University, **Issam A. Mardini,** MD, PhD, is now in the Pulmonary Division, Temple University, School of Medicine.

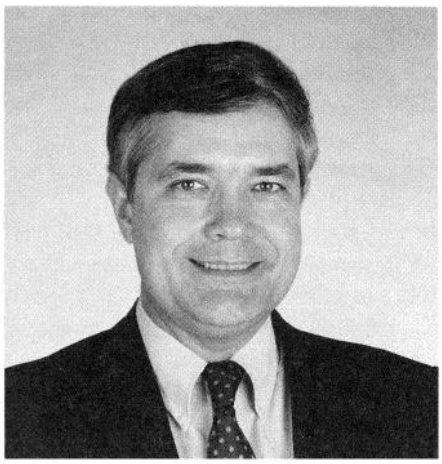
Robert T. Brouillette, MD, has moved to The Montreal Children's Hospital, Division of Neonatology. Brouillette, an APS member, was formerly with the Children's Memorial Hospital in Chicago.

APS member **Gary B. Ellis,** PhD, has been named Director of the Division of Health Promotion and Disease Prevention at the Institute of Medicine of the National Academy of Sciences. He was previously a science policy analyst at the Office of Technology Assessment, US Congress.

APS Members Share in Glaxo Awards

Glaxo announced the launching of a $10 million Cardiovascular Discovery Grants Program. The Discovery Program is designed to forge research partnerships with scientists whose ideas may point the way to discovery of innovative cardiovascular therapeutic agents. APS members among the 20 recipients recommended for funding in 1989 include **Fredric S. Fay,** University of Massachusetts Medical School; **Joe M. McCord,** University of South Alabama College of Medicine; **Bruce Pitt,** University of Pittsburgh School of Medicine; and **David J. Riley,** UMDNS–Robert Wood Johnson Medical School.

Umminger Named Division Director at NSF



Bruce L. Umminger has been appointed Director, Division of Cellular Biosciences (DCB) at the National Science Foundation. From 1985 to 1987 he served as Acting Division Director of DCB. In 1988 he was detailed for one year to the Department of State to serve as Senior Advisor on Health Policy in the Office for International Health Policy. He returned to the Foundation to assume once again the position of Acting Division Director of DCB in October 1988. As an APS member Umminger has served on the Program Advisory Executive Committee and the Program Advisory Committee.

People and Places notices come almost exclusively from information provided by members and interested institutions. To ensure timely publication announcements must be received at least *three months* (by the 5th of the month) before the desired publication date. Send all information to Martin Frank, Editor, *The Physiologist,* APS, 9650 Rockville Pike, Bethesda, MD 20814.

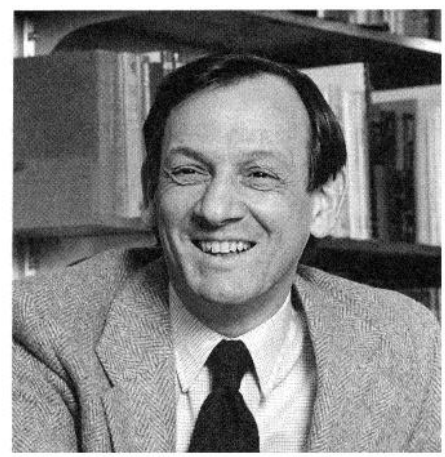
Valtin Receives Top Czechoslovak Physiology Award

Heinz Valtin, MD, Andrew C. Vail Professor and former chair of physiology at the Dartmouth-Hitchcock Medical Center in Hanover, NH, has received the highest award of the Czechoslovak Physiological Society. At ceremonies in Prague, the Purkinje Medal was given to Valtin "in appreciation of his contributions to Czechoslovak physiology."

Valtin, who lives in Norwich, VT, has received international recognition for his work in renal physiology and is a leading authority on how genetics affect some kidney mechanisms. His textbooks on the kidney are widely used in medical schools throughout the world.

Valtin is known worldwide for the development of the Brattleboro rat, a special strain of rat with a hereditary disease called diabetes insipidus. Breeding stock of the rat has been sent around the world; Prague received one of the first shipments. The rat has become a vital tool in the investigation of kidney functions.

Valtin is treasurer of the International Union of Physiological Sciences and has served as chairman of the International Commission on the Kidney. He is a frequent consultant to the US government and the National Board of Medical Examiners.



Animal Issues Gain Momentum in the House While Senate Bills Yet to Find Cosponsors

Interest is growing in the House of Representatives for legislation restricting the use of live animal models for research and testing.

Two House bills—one prohibiting the use of live animals for acute toxicity testing, the other denying funds for animal research should the project be believed to have been attempted previously—have gained a significant number of cosponsors, a barometer for determining Congressional interest in legislative issues.

By the same token two Senate bills—one making break-ins, theft, and vandalism at a research facility a federal crime, the other a companion to the House bill banning the use of live animals for acute toxicity testing—have yet to generate a surge of cosponsors.

One reason for this schizophrenic situation is the push by animal activists for cosponsors of bills they support and the urging of withholding cosponsorship of bills they oppose.

To offset this push there is a need for informing Congressional delegations of the concerns and the effects these bills would have on the scientific community should they be enacted into law. Legislators need to hear both sides of an issue so that they can make decisions that are in the best interest of both their constituency and society. Silence of a constituent is considered to mean tacit approval for the position being taken by a representative or senator.

The chart beginning on page 89 entitled "Actions Speak Louder Than Words" shows Congressional cosponsorship of legislation of interest to physiologists. Now is the time to let your Congressional delegation know where you stand on these bills and to ask them to cosponsor bills you support and not to cosponsor or to withdraw their cosponsorship of bills you oppose.

In making your request tell your senator or representative why you support or oppose a particular bill and how such legislation, if passed, will affect you, your colleagues, students, institution, and community. Also, ask for an explanation should the representative or senator not agree with your views. Moreover, do not accept as an explanation the time-worn phrase, "You may be assured of my continued interest and concern in matters affecting research."

APS is on record supporting the Senate bill (S. 727) that would make break-ins, theft, and vandalism of a research facility a federal crime and encourages its members to ask their senators to join as cosponsors. This is the second time the Congress has considered such a measure, the first dying in a House committee because of a lack of support from the scientific community and a strong letter campaign against such an action by animal activists.

However, APS is opposed to the other Senate bill (S. 891) and its companion bill in the House (H.R. 1676), which would ban all uses of live animals for acute toxicity testing of consumer products. Among the Society's reasons for opposing these bills is that in some safety tests toxicologists must still depend upon live animals as surrogates for humans because there are no reliable alternative methods available at this time. As APS said in its statement last year before a House subcommittee, the Society believes that safety evaluation of human and veterinary drugs, household products, food additives, pesticides, cosmetics, and other chemicals continue to be necessary to protect the public from unknown and unnecessary health risks.

Following are explanations of APS' position on the other bills concerning animals.

The Society does not oppose H.R. 425, which would give the Secretary of the US Department of Agriculture the authority to obtain temporary restraining order or injunction against anyone found dealing in stolen animals or placing the health of an animal in serious jeopardy.

APS is again on record opposing H.R. 560, a bill that has been introduced six times in the last six years, each time dying in a House subcommittee. The bill would establish a National Center for Research Accountability where 20 presidential appointees would review all approved for federal funding research proposals involving the use of animals. Should the proposal be considered duplicative of other work the funding would be denied. The bill also would require the collection in full-text form all biomedical information gained from projects using federal funds. The information would be stored at the National Library of Medicine and made available at cost to all research institutions.

The Society also remains on record opposing H.R. 2345, which would permit anyone to file a civil suit against the US Department of Agriculture for any alleged failure to enforce provisions of the Animal Welfare Act. The bill, if enacted, would give private citizens standing, which is a recognition by the courts that an individual has a tangible stake in litigation.

Animal activists have tried unsuccessfully to be granted standing by the courts, having taken the issue to the US Supreme Court. This is the second Congressional attempt by animal activists to gain standing through legislative means since being denied recognition by the judiciary as having the right to sue on behalf of any animal for an alleged lack of enforcement of the Animal Welfare Act.

Actions Speak Louder Than Words

Cosponsorship of legislation is one of the best ways to determine where a member of Congress stands on an issue.

The 'x' indicates those senators (bold-face type) and representatives cosponsoring legislation that would restrict the use of laboratory animals for purposes of research, education, and testing. The '✓' indicates cosponsorship of legislation that APS can support. Bills of interest to physiologists are

Senate—**S. 727**: (✓) "Animal Research Facilities Protection Act of 1989" makes break-ins and vandalism of research facilities a federal crime. **S. 891**: (x) "Consumer Products Safe Testing Act" seeks to prohibit the use of live animals for acute toxicity testing.

House—**H.R. 425**: (✓) "Animal Welfare Protection Act of 1989" provides the Secretary of Agriculture with authority to obtain temporary restraining orders and injunctions against persons dealing in stolen animals. **H.R. 560**: (x) "The Information Dissemination & Research Accountability Act" establishes a National Center for Research Accountability that would serve as a repository for full-text research data and would review all approved research grants involving live animals and deny funding should the research be deemed as having been done or is being done. **H.R. 1676**: (x) "Consumer Products Safe Testing Act" is the same as S. 891. **H.R. 2345**: (x) This would amend the Animal Welfare Act to grant individuals the right to file civil suits against the US Department of Agriculture for any alleged failure to enforce provisions of Act.

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
ALABAMA						
Heflin (D)	✓					
Shelby (D)						
Callahan (R)						
Dickinson (R)						
Browder (D)						
Bevil (D)						
Flippo (D)						
Erdreich (D)						
Harris (D)						
ALASKA						
Stevens (R)	✓					
Murkowski (R)						
Young (R)					x	
ARIZONA						
DeConcini (D)						
McCain (R)						
Rhodes (R)						
Udall (D)						
Stump (R)						
Kyl (R)						
Kolbe (R)						
ARKANSAS						
Bumpers (D)						
Pryor (D)	✓					
Alexander (D)						
Robinson (D)			✓			
Hammerschmidt (R)						
Anthony (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
CALIFORNIA						
Cranston (D)						
Wilson (R)						
Bosco (D)				x	x	
Herger (R)						
Matsui (D)						
Fazio (D)						
Pelosi (D)			✓		x	
Boxer (D)				x	x	
Miller (D)						
Dellums (D)			✓	x		
Stark (D)						
Edwards (D)				x	x	
Lantos (D)				x		x
Campbell (R)			✓			
Mineta (D)				x		
Shumway (R)						
Panetta (D)						
Pashayan (R)						
Lehman (D)						
Lagomarsino (R)			✓			
Thomas (R)						
Gallegly (R)			✓			
Moorhead (R)						
Beilenson (D)						
Waxman (D)						
Roybal (D)						
Berman (D)						
Levine (D)						
Dixon (D)			✓		x	
Hawkins (D)				x	x	
Martinez (D)			✓	x	x	x
Dymally (D)			✓	x		
Anderson (D)					x	
Dreier (R)						
Torres (D)						x
Lewis (R)						
Brown (D)					x	
McCandless (R)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
Dornan (R)			✓	x		
Dannemeyer (R)						
Cox (R)						
Lowery (R)						
Rohrabacher (R)						
Packard (R)						
Bates (D)			✓	x	x	
Hunter (R)						
COLORADO						
Armstrong (R)						
Wirth (D)						
Schroeder (D)						
Skaggs (D)						
Campbell (D)						
Brown (R)						
Hefley (R)						
Schaefer (R)						
CONNECTICUT						
Dodd (D)	✓					
Lieberman (D)						
Kennelly (D)						
Gejdenson (D)				x		
Morrison (D)					x	
Shays (R)			✓	x	x	
Rowland (R)						
Johnson (R)						
DELAWARE						
Roth (R)						
Biden (D)						
Carper (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
FLORIDA						
Graham (D)						
Mack (R)						
Hutto (D)						
Grant (R)						
Bennett (D)						x
James (R)						
McCollum (R)						
Stearns (R)						
Gibbons (D)			✓		x	x
Young (R)			✓	x		
Bilirakis (R)						
Ireland (R)						
Nelson (D)						
Lewis (R)			✓			
Goss (R)						
Johnston (D)						
Shaw (R)			✓			
Smith (D)			✓	x		
Lehman (D)						
Fascell (D)						
GEORGIA						
Nunn (D)						
Fowler (D)						
Thomas (D)			✓			
Hatcher (D)						
Ray (D)						
Jones (D)						
Lewis (D)			✓	x	x	
Gingrich (R)						
Darden (D)						
Rowland (D)						
Jenkins (D)						
Barnard (D)						
HAWAII						
Inouye (D)	✓					
Matsunaga (D)						
Saiki (R)				x		
Akaka (D)				x		
IDAHO						
McClure (R)						
Symms (R)	✓					
Craig (R)						
Stallings (D)						
ILLINOIS						
Dixon (D)						
Simon (D)						
Hayes (D)					x	x
Savage (D)					x	
Russo (D)			✓	x	x	
Sangmeister (D)						
Lipinski (D)				x	x	x
Hyde (R)				x	x	
Collins (D)			✓	x	x	
Rostenkowski (D)						
Yates (D)			✓	x	x	
Porter (R)						
Annunzio (D)						
Crane (R)						
Fawell (R)						
Hastert (R)						
Madigan (R)						
Martin (R)						
Evans (D)						
Michel (R)						
Bruce (D)						
Durbin (D)						
Costello (D)				x		
Poshard (D)						
INDIANA						
Lugar (R)	✓					
Coats (R)	✓					
Visclosky (D)						
Sharp (D)						
Hiler (R)						
Long (D)						
Jontz (D)						
Burton (R)				x		
Myers (R)						
McCloskey (D)					x	
Hamilton (D)						
Jacobs (D)			✓	x	x	x
IOWA						
Grassley (R)						
Harkin (D)						
Leach (R)						
Tauke (R)						
Nagle (D)						
Smith (D)						
Lightfoot (R)						
Grandy (R)						
KANSAS						
Dole (R)						
Kassebaum (R)	✓					
Roberts (R)						
Slattery (D)						
Meyers (R)			✓			
Glickman (D)						
Whittaker (R)						
KENTUCKY						
Ford (D)						
McConnell (R)						
Hubbard (D)						
Natcher (D)						
Mazzoli (D)						
Bunning (R)						
Rogers (R)						
Hopkins (D)						
Perkins (D)					x	
LOUISIANA						
Johnston (D)						
Breaux (D)						
Livingston (R)						
Boggs (D)						
Tauzin (D)						
McCrery (R)						
Huckaby (D)						
Baker (R)						
Hayes (D)						
Holloway (R)						
MAINE						
Cohen (R)						
Mitchell (D)						
Brennen (D)						
Snowe (R)				x		
MARYLAND						
Sarbanes (D)						
Mikulski (D)						
Dyson (D)						
Bentley (R)			✓	x	x	
Cardin (D)			✓		x	
McMillen (D)						
Hoyer (D)						
Byron (D)						
Mfume (D)				x		
Morella (R)					x	
MASSACHUSETTS						
Kennedy (D)						
Kerry (D)						
Conte (R)						
Neal (D)					x	
Early (D)						
Frank (D)					x	
Atkins (D)			✓	x	x	
Mavroules (D)					x	
Markey (D)				x	x	
Kennedy (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
Moakley (D)						
Studds (D)						
Donnelly (D)					x	
MICHIGAN						
Riegle (D)						
Levin (D)						
Conyers (D)				x	x	
Pursell (R)			✓			
Wolpe (D)						
Upton (R)				x	x	
Henry (R)						
Carr (D)						
Kildee (D)			✓			
Traxler (D)						
Vander Jagt (R)						
Schuette (R)						
Davis (R)						
Bonior (D)					x	
Crockett (D)						
Hertel (D)						
Ford (D)						
Dingell (D)						
Levin (D)						
Broomfield (R)					x	
MINNESOTA						
Durenberger (R)						
Boschwitz (R)						
Penny (D)						
Weber (R)						
Frenzel (R)						
Vento (D)						
Sabo (D)						
Sikorski (D)				x		
Stangeland (R)						
Oberstar (D)						
MISSISSIPPI						
Cochran (R)	✓					
Lott (R)						
Whitten (D)						
Espy (D)						
Montgomery (D)						
Parker (D)						
Smith (R)						
MISSOURI						
Danforth (R)						
Bond (R)						
Clay (D)				x	x	
Buechner (R)			✓			
Gephardt (D)						
Skelton (D)						
Wheat (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
Coleman (R)						
Hancock (R)						
Emerson (R)						
Volkmer (D)						
MONTANA						
Baucus (D)						
Burns (R)						
Williams (D)					x	
Marlenee (R)						
NEBRASKA						
Exon (D)						
Kerry (D)						
Bereuter (R)						
Hoagland (D)						
Smith (R)						
NEVADA						
Reid (D)		x				
Bryan (D)						
Bilbray (D)						
Vucanovich (R)						
NEW HAMPSHIRE						
Humphrey (R)						
Rudman (R)						
Smith (R)			✓	x	x	
Douglas (R)						
NEW JERSEY						
Bradley (D)						
Lautenberg (D)						
Florio (D)			✓	x	x	
Hughes (D)			✓	x	x	
Pallone (D)			✓	x	x	
Smith (R)						
Roukema (R)						
Dwyer (D)			✓	x	x	
Rinaldo (R)			✓	x	x	
Roe (D)			✓	x	x	
Torricelli (D)				x	x	
Payne (D)				x		
Gallo (R)				x	x	
Courter (R)						
Saxton (R)			✓	x		
Guarini (D)			✓	x	x	
NEW MEXICO						
Domenici (R)						
Bingaman (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
Schiff (R)						
Skeen (R)						
Richardson (D)						
NEW YORK						
Moynihan (D)						
D'Amato (R)						
Hochbrueckner (D)						
Downey (D)				x		
Mrazek (D)			✓	x	x	
Lent (R)						
McGrath (R)			✓	x	x	
Flake (D)						
Ackerman (D)				x	x	
Scheuer (D)					x	
Manton (D)				x	x	x
Schumer (D)				x	x	
Towns (D)			✓	x	x	
Owens (D)			✓	x	x	x
Solarz (D)			✓	x	x	
Molinari (R)						
Green (R)						
Rangel (D)						
Weiss (D)			✓		x	
Garcia (D)			✓		x	
Engel (D)						
Lowey (D)						
Fish (R)					x	
Gilman (R)				x		
McNulty (D)						
Solomon (R)						
Boehlert (R)						
Martin (R)						
Walsh (R)				x		
McHugh (D)						
Horton (R)				x		
Slaughter (D)						
Paxon (R)						
LaFalce (D)						
Nowak (D)			✓		x	
Houghton (R)				x		
NORTH CAROLINA						
Helms (R)	✓					
Sanford (D)						
Jones (D)						
Valentine (D)						
Lancaster (D)						
Price (D)						
Neal (D)						
Coble (R)						
Rose (D)					x	x
Hefner (D)						
McMillan (R)						
Ballenger (R)						
Clarke (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
NORTH DAKOTA						
Burdick (D)						
Conrad (D)	✓					
Dorgan (D)						
OHIO						
Glenn (D)						
Metzenbaum (D)						
Luken (D)					x	
Gradison (R)						
Hall (D)						
Oxley (R)						
Gillmor (R)						
McEwen (R)						
DeWine (R)						
Lukens (R)						
Kaptur (D)				x	x	
Miller (R)			✓			
Eckart (D)						
Kasich (R)						
Pease (D)				x		
Sawyer (D)						
Wylie (R)						
Regula (R)				x		
Traficant (D)			✓	x	x	x
Applegate (D)						
Feighan (D)						
Oakar (D)						
Stokes (D)						
OKLAHOMA						
Boren (D)	✓					
Nickles (R)						
Inhofe (R)						
Synar (D)					x	
Watkins (D)						
McCurdy (D)						
Edwards (R)			✓			
English (D)						
OREGON						
Hatfield (R)						
Packwood (R)						
AuCoin (D)						
Smith (R)						
Wyden (D)						
DeFazio (D)			✓		x	
Smith (R)					x	
PENNSYLVANIA						
Heinz (R)						
Specter (R)						
Foglietta (D)			✓	x	x	
Gray (D)						
Borski (D)			✓	x		
Kolter (D)			✓			x
Schulze (R)						
Yatron (D)					x	
Weldon (R)						
Kostmayer (D)			✓	x	x	
Shuster (R)						
McDade (R)						
Kanjorski (D)						
Murtha (D)						
Coughlin (R)						
Coyne (D)						
Ritter (R)						
Walker (R)						
Gekas (R)						
Walgren (D)					x	
Goodling (R)				x		
Gaydos (D)						
Ridge (R)						
Murphy (D)						
Clinger (R)						
RHODE ISLAND						
Pell (D)						
Chafee (R)						
Machtley (R)						
Schneider (R)				x	x	
SOUTH CAROLINA						
Thurmond (R)	✓					
Hollings (D)						
Ravenel (R)				x	x	x
Spence (R)						
Derrick (D)						
Patterson (D)						
Spratt (D)						
Tallon (D)						
SOUTH DAKOTA						
Pressler (R)						
Daschle (D)						
Johnson (D)						
TENNESSEE						
Sasser (D)						
Gore (D)						
Quillen (R)						
Duncan (R)						
Lloyd (D)						
Cooper (D)						
Clement (D)			✓			
Gordon (D)						
Sundquist (R)						
Tanner (D)						
Ford (D)						
TEXAS						
Bentsen (D)						
Gramm (R)						
Chapman (D)				x		
Wilson (D)				x	x	x
Bartlett (R)						
Hall (D)						
Bryant (D)					x	
Barton (R)						
Archer (R)						
Fields (R)						
Brooks (D)						
Pickle (D)						
Leath (D)						
Sarpalius (D)						
Laughlin (D)						
de la Garza (D)						
Coleman (D)						
Stenholm (D)						
Leland (D)						
Combest (R)						
Gonzalez (D)						
Smith (R)						
DeLay (R)						
Bustamante (D)						
Frost (D)						
Andrews (D)						
Armey (R)						
Ortiz (D)						
UTAH						
Garn (R)	✓					
Hatch (R)	✓					
Hansen (R)						
Owens (D)						
Nielson (R)						
VERMONT						
Leahy (D)						
Jeffords (R)						
Smith (R)						
VIRGINIA						
Warner (R)						
Robb (D)						
Bateman (R)						
Pickett (D)						
Bliley (R)						
Sisiky (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
Payne (D)						
Olin (D)						
Slaughter (R)						
Parris (R)				x		
Boucher (D)						
Wolf (R)						
WASHINGTON						
Adams (D)						
Gorton (R)						
Miller (R)					x	
Swift (D)						
Unsoeld (D)						
Morrison (R)						
Foley (D)						
Dicks (D)					x	
McDermott (D)						
Chandler (R)			✓		x	
WEST VIRGINIA						
Byrd (D)						
Rockefeller (D)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
Mollohan (D)			✓			
Staggers (D)						
Wise (D)						
Rahall (D)			✓		x	
WISCONSIN						
Kasten (R)						
Kohl (D)						
Aspin (D)						
Kastenmeier (D)			✓		x	
Gunderson (R)						
Kleczka (D)			✓		x	x
Moody (D)			✓		x	
Petri (R)						
Obey (D)						
Roth (R)			✓			
Sensenbrenner (R)						
WYOMING						
Wallop (R)						
Simpson (R)						
Thomas (R)						

	S. 727	S. 891	H.R. 425	H.R. 560	H.R. 1676	H.R. 2345
AMERICAN SAMOA						
Faleomavaega (D)						
DISTRICT OF COLUMBIA						
Fauntroy (D)			✓	x	x	
GUAM						
Blaz (R)						
PUERTO RICO						
Fuster (D)					x	
VIRGIN ISLANDS						
de Lugo (D)			✓		x	

APS Urges Congress to Support NASA Life Sciences, Primate Centers

The American Physiological Society has urged Congressional appropriations committees not to cut back on proposed budget recommendations for both the National Aeronautics and Space Administration's Life Sciences Division and the seven regional primate centers.

A letter concerning the Life Sciences Division was sent to members of both the House and Senate subcommittees on HUD and independent agencies. A letter concerning the primate centers was sent to the full membership of the House and Senate appropriations committees and to the Congressional delegations in the seven states where the centers are located.

Text of the two letters follows.

May 4, 1989

The American Physiological Society urges the Subcommittee on HUD and Independent Agencies to take the long view in its deliberations on the 1990 fiscal year appropriations for the Life Sciences Division of the National Aeronautics and Space Administration (NASA).

The Bush Administration has proposed a major increase in the Life Sciences Division budget as a means to enable NASA to carry on with the 1.8m centrifuge; prepare for the Space Biology Initiative; continue planning for the Lifesat free flyer mission; qualify crews for extended work tours on the space station; and begin efforts to qualify pilots for shuttle landings following long duration flights.

It is the latter that is of greatest concern to the Society inasmuch as it is a new initiative and, therefore, in a period of fiscal constraint a most likely item to be considered for deletion by an appropriations committee.

The need for taking the long view is based on the fact that the Life Sciences Division must begin at this time the pro-

gram that will determine whether pilots will have sufficient muscle coordination to land the shuttle after prolonged space flights, scheduled to begin in 1992. Until now the longest shuttle flight has been 10 days and no one knows what the effects of weightlessness are on pilot coordination for flights now scheduled for 16 and 28 days.

If the coordination studies are not started during the next fiscal year, the prolonged space flights will have to be pushed back until such studies have been completed to assure crew safety.

In light of last year's major cuts in the Life Sciences Division's appropriation, the American Physiological Society strongly urges the subcommittee during its deliberations to give careful consideration to NASA's proposed flight schedules and the roles that must be played prior to these flights by the Life Sciences Division.

Sincerely,

Martin Frank, Ph.D.
Executive Director

May 23, 1989

This letter is on behalf of the members of the American Physiological Society who are concerned about the future of a national resource essential to biomedical research—the seven federally sponsored regional primate centers.

In 1960 the Congress created the Primate Research Centers as a means to provide the nation's biomedical research scientists using nonhuman primates with the resources and expertise necessary in the continuing search to find treatment, cure, and prevention of human illnesses, including Alzheimer's Disease, AIDS, and Parkinson Disease.

The centers are supported by five-year core grants from the National Institutes of Health (NIH) and the scientists at the centers are supported by competing grants from both NIH and the National Science Foundation. Last year the core grants for both Oregon and Wisconsin centers were reviewed for renewal by an NIH panel, which recommended increases in funding for continued research in areas of neuroscience, AIDS, and reproductive biology.

Now, the seven centers have been informed that their 1989–90 support budgets are to be reduced by 2.7 percent from the existing 1988–89 budgets and that a reduction of 1.6 percent should be anticipated for the 1990–91 budgets. This is the first time in the history of the centers that the existing budgets rather than the proposed budgets have been cut back and when these reductions are compounded by inflation and the recommended budget increases for renewed core grants, the overall budget reduction could run as much as 36 percent for some centers.

This loss of support funds already has resulted in a reduction of personnel, including research scientists at the Oregon center. Further cutbacks will mean additional losses of those who are now active in the conduct of research in organ transplantation, cardiovascular disease, behavioral research related to mental health problems, reproductive endocrinology, as well as specific diseases that effect both human and animal health.

It is the plea of the American Physiological Society that the Congress not turn its back on the Primate Research Centers, but provide the centers with the necessary core funds. These seven NIH-supported centers are vital to the nation's universities, hospitals, and institutions in the conduct of research. Failure to provide the necessary support funds not only will result in a setback to the current research endeavors through the loss of technical and scientific personnel, but also will place in jeopardy the existence of a vital national resource essential to biomedical research.

Sincerely,

Vernon S. Bishop, Ph.D.
President

Call, Don't Write

Everybody, it seems, is writing to their congressman, and as a result don't expect a reply anytime soon.

The Office of the Postmaster for the House of Representatives has been inundated with constituent mail, and despite a 60-hour work week, letters, mailgrams, and packages have been known to take a week to be sorted and delivered to House offices.

Incoming mail for House members has increased from 14.5 million pieces in 1972 to 156.6 million pieces in 1988. At the current rate House members will receive 391.5 million pieces of mail in 1989. (The Senate mail office is not experiencing a similar increase, and constituent mail is delivered on the day it is received.)

Most of the mail being sent to House members is constituent concerns about ethics, Medicare, gun control, taxes, abortion, and animal rights.

Public Opinion Says Fraud in Science is High, Use of Lab Animals is OK

A random sample of 1,500 adults shows that the majority of Americans believe there is a fair amount of scientific fraud by medical researchers, that the use of laboratory animals is necessary for medical progress, and that funding for research should stay about the same.

The survey by the Gallup Organization was commissioned by the American Medical Association.

In response to questions as to scientific fraud or misrepresentation, 41% said that they believed "a fair amount of fraud" is occurring in medical research, and another 17% said that "a lot of fraud" exists. Thirty percent said that they believed there was little or almost no fraud happening in scientific research.

As for the use of laboratory animals in research, the majority of the respondents agreed that animal models are necessary for medical progress and support the use of animals for such purposes, including unwanted pound animals.

In general terms two out of three respondents (64%) support the use of animals in research, of which more than one-half of the supporters (36%) said they "strongly support" such research. Of the 29% opposed to the use of animals in research, 23% said they "strongly oppose" such research. However, some of the opposition must be in principle, inasmuch as 77% of the respondents also said that animal research is necessary for progress in medicine. Also, 71% favored allowing researchers to use animals that otherwise would be euthanized at the pounds.

Support for animal research geographically is very high in the Pacific and Rocky Mountain regions (71%) and low in the New England, Middle Atlantic, and East South Central States (58%).

As for federal funding of research projects, 50% said current levels are adequate and should be maintained, and 37% said that funding should be increased. Four percent said such funding should be decreased.

ILAR Sets New Guidelines for Precollege Lab Animal Use

The National Academy of Sciences' Institute of Laboratory Animal Resources (ILAR) has issued new principles and guidelines for the use of animal in precollege education.

The ILAR guidelines are more stringent than are the widely used guidelines of the National Science Teachers Association. ILAR Chairman Steven Pakes said the guidelines are more in line with the use of animals in medical school education, adding, "The point isn't to stop all inquiry. This issue is the appropriate use of animals at that [precollege] level."

ILAR, which is a part of the Academy's National Research Council, views the guidelines as a means of stimulating students and teachers to consider alternatives to experiments with animals and to plan more carefully when animals are studied.

Guidelines

The humane study of animals in precollege education can provide important learning experiences in science and ethics and should be encouraged. Maintaining classroom pets in preschool and grade school can teach respect for other species, as well as proper animal husbandry practices. Introduction of secondary school students to animal studies in closely supervised settings can reinforce those early lessons and teach the principles of humane care and use of animals in scientific inquiry. The National Research Council recommends compliance with the following principles whenever animals are used in precollege education or in science fair projects.

PRINCIPLE I: Observational and natural history studies that are not intrusive (that is, do not interfere with an animal's health or well-being or cause it discomfort) are encouraged for all classes of organisms. When an intrusive study of a living organism is deemed appropriate, consideration should be given first to using plants (including lower plants such as yeast and fungi) and invertebrates with no nervous systems or with primitive ones (including protozoa, planaria, and insects). Intrusive studies of invertebrates with advanced nervous systems (such as octopi) and vertebrates should be used only when lower invertebrates are not suitable and only under the conditions stated below in *Principle X.*

PRINCIPLE II: Supervision shall be provided by individuals who are knowledgeable about and experienced with the health, husbandry, care, and handling of the animal spe-

cies used and who understand applicable laws, regulations, and policies.

PRINCIPLE III: Appropriate care for animals must be provided daily, including weekends, holidays, and other times when school is not in session. This care must include

a. nutritious food and clean, fresh water;
b. clean housing with space and enrichment suitable for normal species behaviors; and
c. temperature and lighting appropriate for the species.

PRINCIPLE IV: Animals should be healthy and free of diseases that can be transmitted to humans or to other animals. Veterinary care must be provided as needed.

PRINCIPLE V: Students and teachers should report immediately to the school health authority all scratches, bites, and other injuries; allergies; or illnesses.

PRINCIPLE VI: Prior to obtaining animals for educational purposes, it is imperative that the school develop a plan for their procurement and ultimate disposition. Animals must not be captured from or released into the wild without the approval of the responsible wildlife and public health officials. When euthanasia is necessary, it should be performed in accordance with the most recent recommendations of the American Veterinary Medical Association's *Panel Report on Euthanasia.* It should be performed only by someone trained in the appropriate technique.

PRINCIPLE VII: Students shall not conduct experimental procedures on animals that

a. are likely to cause pain or discomfort or interfere with an animal's health or well-being;
b. induce nutritional deficiencies or toxicities; or
c. expose animals to microorganisms, ionizing radiation, cancer-producing agents, or any other harmful drugs or chemicals capable of causing disease, injury, or birth defects in humans or animals.

In general, procedures that cause pain in humans are considered to cause pain in other vertebrates.

PRINCIPLE VIII: Experiments on avian embryos that might result in abnormal chicks or in chicks that might experience pain or discomfort shall be terminated 72 hours prior to the expected date of hatching. The eggs shall be destroyed to prevent inadvertent hatching.

PRINCIPLE IX: Behavioral conditioning studies shall not involve aversive stimuli. In studies using positive reinforcement, animals should not be deprived of water; food deprivation intervals should be appropriate for the species but should not continue longer than 24 hours.

PRINCIPLE X: A plan for conducting an experiment with living animals must be prepared in writing and approved prior to initiating the experiment or to obtaining the animals. Proper experimental design of projects and concern for animal welfare are important learning experiences and contribute to respect for and appropriate care of animals. The plan shall be reviewed by a committee composed of individuals who have the knowledge to understand and evaluate it and who have the authority to approve or disapprove it. The written plan should include the following:

a. a statement of the specific hypotheses or principles to be tested, illustrated, or taught;
b. a summary of what is known about the subject under study, including references;
c. a justification for the use of the species selected and consideration of why a lower vertebrate or invertebrate cannot be used; and
d. a detailed description of the methods and procedures to be used, including experimental design; data analysis; and all aspects of animal procurement, care, housing, use, and disposal.

EXCEPTIONS: Exceptions to principles VII-X may be granted under special circumstances by a panel appointed by the school principal or his or her designee. This panel should consist of at least three individuals including a science teacher, a teacher of a nonscience subject, and a scientist or veterinarian who has expertise in the subject matter involved. At least one panel member should not be affiliated with the school or science fair, and none should be a member of the student's family.

William M. Samuels

So They Say . . .

"If we don't speak out about the benefits of animal research, about how we do things, and if we don't take care of our animals, I think the end is in sight. There will be no animals used for biomedical research, period."

Richard Traystman
The Johns Hopkins University
in *The Scientist*

APS Responds to APHIS Proposed Regulations for Lab Animal Welfare

The American Physiological Society has sent letters of comment concerning the proposed rules for the implementation of the 1985 amendments to the Animal Welfare Act.

The letters to the US Department of Agriculture's Animal and Plant Health Inspection Service told of the Society's concerns with the proposed rules, which are restrictive, costly, and do nothing to improve the welfare of animals. Copies of the letters also were sent to the Office of Management and Budget, US Department of Health and Human Services, and the National Institutes of Health.

The text of the letters follow.

May 12, 1989

Helene R. Wright
Chief, Regulatory Analysis and Development Staff
PPD, APHIS, USDA
Room 1000, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782

Dear Ms. Wright:

The comments in this letter are in reference to Docket No. 88-013, the proposed rules for the Animal and Plant Health Inspection Service's (APHIS) implementation of the Animal Welfare Act amendments enacted by Public Law 99-198, "The Food Security Act of 1985."

The purpose of this letter is to cite the concerns of the American Physiological Society regarding Parts I and II of the proposed rules. The Society, which is the nation's senior biomedical sciences society, includes Nobel laureates among its 6,600 members who are engaged in research and educational programs involving the use of live animal models.

Physiologists have a long-standing interest in humane care of laboratory animals, evident by the fact that the Society was the first to establish guidelines for the care and treatment of animals used in research and education.

The society believes humane care and treatment and the minimizing of pain or distress in laboratory animals are vital for productive research. Support and respect for humanitarian concerns for both human and animal welfare continues to be of paramount importance to physiologists and are among the reasons why the Society was one of the first to support amendments to the Animal Welfare Act.

An expressed Congressional intent of the amendments is to ensure that all animals receive humane treatment and that no animal experiences unnecessary pain or discomfort during research procedures. The Congress also determined that the Secretary of Agriculture shall take no action, either direct or promulgated, that would interfere with research and experimentation. The Society agrees wholeheartedly with the intent of the Congress and believes the proposed rules should be limited to animals subject to pain and/or discomfort.

Therefore, it is the Society's recommendation that research involving non-survival surgery of fully anesthetized animals be exempt from the proposed rules. The welfare of laboratory animals can be better served if the energies of the institutional animal care and use committees are concentrated on research involving survival surgery where there is the possibility for animal pain and/or discomfort. This is both the intended and appropriate roles for the animal care and use committees.

Also of major concern to the Society is APHIS' continued efforts to give animal care and use committees roles that exceed statutory authority, such as the proposed rule that any (research) procedures and practices involving anmals must be approved by the institutional animal care and use committee "prior to the start of research, testing, or teaching involving an animal;". The statute (Section 13 (6) (A) (i) of PL 99-198) does not authorize research project review by the committee nor is prior committee approval of research procedures and practices a requirement of the Animal Welfare Act. This is the responsibility of the peer review committees and the granting agencies.

Moreover, Section 13 is explicit in its language regarding this protection of research prerogatives, stating ". . . nothing in this Act shall be construed as authorizing the Secretary to promulgate rules, regulations, or orders with regard to the performance of actual research or experimentation by a research facility as determined by such research facility." The Society's recommendation is that references to prior approval be deleted from the proposed rules.

The Society is concerned with the extent to which the proposed rules continue to differ from the Public Health Service's "Policy on the Humane Care and Use of Laboratory Animals." The Congress specifically charged the Secretary of Agriculture to consult with the Secretary of the Department of Health and Human Services to assure there is agreement in the definitions and rules for laboratory animal use and care.

This inconsistency of rules between agencies can only result in additional expense to the Department of Agriculture, the Public Health Service, and research institutions; confusion and conflict for the scientists and the animal care and use committees; and interference with the efficient conduct of research, none of which leads to improving the welfare of animals.

The Society is dismayed by the APHIS admission that the rules it is proposing will have an immediate cost of more than a billion dollars of which the brunt of the expense will be borne by private sector institutions and will add an annual cost of nearly a billion dollars to maintain compliance with the proposed rules.

Most of these costs are due to added burdens APHIS has placed upon research institutions, the scientists, and the animal care and use committees, such as increased reporting requirements, excessive intervention into institutional prerogatives, and the shifting of resources from the laboratory to the support of an institutional bureaucracy.

Such costs do not improve the health and welfare of a single laboratory animal and obstruct rather than facilitate research by diverting funds from productive investigations. Furthermore, many experiments that would improve the health of both humans and animals will never be done because of the diversion of funds to maintain compliance.

In addition to the general concerns expressed above, the Society has the following specific concerns:

Training [Subpart C 2.30 (i) (4) (i-xi)]. APHIS again goes beyond the intent of Congress by prescribing detailed training requirements and, thus, trespasses upon basic American tenets of academic freedom that give educational institutions the prerogative and the responsibility to determine what training is required to achieve stated goals. It is not APHIS' prerogative to dictate educational requirements to educational institutions, which represent the vast majority of the nation's research facilities. APHIS's role is to identify the goals of training mandated by the statute, thereby permitting institutions of higher learning to fulfill their responsibility of determining the training requirements to achieve those goals.

Painful Procedure [Supplemental Information]. The proposed definition for painful procedure says, ". . . investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals." It is the Society's belief that this definition is not only misleading, but also permits subjective decisions by the animal care and use committees when in fact some painful experiences for humans are not painful experiences for some animals. For example, coronary occlusion is painful to humans, but has not been shown to be painful to dogs. The same also is true for indwelling subcutaneous needle electrodes.

Attending Veterinarian [Subpart C 2.30 (e) (2)]. The rule proposes that the attending veterinarian must be consulted by the principal investigator during actual research. Again APHIS proposes a rule that exceeds statutory authority as the law requires that the veterinarian be consulted only during the planning of procedures. It is the principal investigator's prerogative to seek consultation during actual research; to require such consultation places the veterinarian and the principal investigator in adversarial roles.

The care of animals and the review of the animal care records are the responsibilities of the veterinarian and the animal care committee; research is the responsibility of the scientist.

Inspections [Subpart C 2.35 (b) (1) (vi)]. The proposed rule requires that the semi-annual inspections of animal facilities be accomplished within a 30-day period and the reports for certification be filed within 10 working days. Most major research institutions have several hundred separate animal sites, thus making this a near impossible task for an animal care and use committee to accomplish within the time constraints. This proposed rule is unreasonable as it escalates the inspection requirements to fulltime jobs twice a year for the committee members. Not only does this remove the committee members from their normal employment responsibilities, but it also represents a loss of work time for individuals whose animal sites are being inspected. Such concentrated time demands will not only discourage qualified individuals from the public sector from serving on the institution's animal care and use committee, but also will deter individuals employed by the institution.

The Society recommends that research institutions be permitted to phase the inspection of the animal facilities at the discretion of the institution, so long as the stated requirement of semi-annual inspections are met.

Access [Subpart C 2.30 (c)]. The rule proposes that each research facility shall provide the animal care and use committee members and the veterinarian with the authority to enter all animal areas at any time. Such a rule would not only violate Section 13 of the Act, which prohibits interference with research, but it also could be disruptive to active research, such as survival surgery, or ongoing research, such as controlled light cycles.

The Society's recommendation as a means to avoid interference with research is that the rule be modified so that inspections of a study area are limited to times when there would be no interference with the research being conducted. This can be determined by prior consultation with the investigator.

Survival Surgery [Subpart C 2.30 (e) (7)]. The rule proposes that all survival surgeries be conducted only in facilities intended for that purpose and operated and maintained under aseptic conditions. The Society disagrees that all survival surgery must be conducted in facilities intended for such purposes inasmuch as there is solid evidence showing that good aseptic surgical techniques do not depend upon dedicated surgical suites for aseptic surgical results.

Euthanasia [Supplemental Information]. The proposed rules for euthanasia urge reliance on the American Veterinary

Medical Association's current "Panel on Euthanasia." Because there is a valid scientific disagreement on the Panel's recommended procedure for decapitation, the Society recommends the Panel's previous (1978) recommendation for decapitation be followed until the debate is resolved.

Photographs [Subpart I 2.126 (5)]. The proposed rule would permit APHIS inspectors "to take photographs to document conditions and/or areas of noncompliance in the facility." Because photographs are available through the Freedom of Information Act and could be used as a technique to harass institutions, it is the Society's recommendation that photographs be limited to areas of repeated noncompliance rather than first-time failures which may be corrected quickly.

Missing Animals [Subpart I 2.128 (a) (1-2)]. The proposed rule grants law officers the right to enter animal facilities to look for animals reported missing. The Society questions the constitutionality of such action inasmuch as there are no stated requirements for obtaining a search warrant. The Society believes such entry would be illegal and a denial of constitutional rights.

Procurement [Subpart I 2.321 (a-e)]. The proposed rule would deny procurement of random source dogs and cats by Class B dealers. This is yet another example of APHIS going beyond statutory authority and proposing a rule that would increase the cost of research for no proven purpose. The rule proposed is patterned after the "Pet Theft Act of 1988," which died in the 100th Congress. The Society recommends that this section be deleted until the intent of the Congress has been determined by legislative authority.

In reviewing the proposed rules the Society is disturbed by the overall tenor of the rules which are negative in tone and adversarial in attitude, which could destroy a collegial climate between the researchers and APHIS. Nowhere in the proposed rules does APHIS make mention of the rights of researchers, despite that such rights are provided for in Sections 13 and 27 of the Act; nor does APHIS provide research institutions any protection from the public for disclosure of unsubstantiated claims.

Moreover, APHIS states in the Supplementary Information that it does not believe that regulations providing such protections are warranted. Combine this attitude with the section on procedures for personnel to report violations and the repeated references to facilities, then APHIS' lack of appreciation and understanding for the constituency it is charged to serve becomes obvious.

The Society appreciates the opportunity to make known its concerns and the concerns of the nation's physiologists regarding the rules proposed for the implementation of the 1985 amendments to the Animal Welfare Act.

Sincerely,
Vernon S. Bishop, PhD
President

July 11, 1989

Dear Ms. Wright:

This letter of comment is the American Physiological Society's response to Docket No. 87-004, commonly known as Part III of the rules proposed by the Animal and Plant Health Inspection Service (APHIS) for implementing the Animal Welfare Act amendments enacted by the "Food Security Act of 1985" (Public Law 99-198).

The Society expressed the concerns of its 6,600 members regarding Parts I and II of the proposed rules in a letter of comment dated May 12, 1989. As stated in that letter, physiologists have a long-standing interest in humane care of laboratory animals and support and respect humanitarian concerns for both human and animal welfare. Moreover, the purpose of the Society's comments are not to subvert the proposed rules but rather make then effectual for the welfare of laboratory animals without interfering with research.

It is an accepted principle of science that optimal physiological and psychological well-being of a laboratory animal enhances research and is essential for its validity. However, an environment of well-being for laboratory animals can not be achieved by a centralized regulatory process based on engineering standards, such as the rules proposed by APHIS. Rather than promulgating engineering or design standards that have neither scientific basis, reason, nor salutary effect on laboratory animal welfare, APHIS should develop performance standards wherein animal welfare decisions are permitted to be determined on a case-by-case basis by those who are primarily responsible for animal welfare: the principal investigator and the attending veterinarian. The Society believes that performance standards based on experimental results and observations are both practical and reasonable for assuring the desired environment for laboratory animals.

Furthermore, to issue standards, such as housing requirements, that do not take into consideration the species and their habits not only impedes research and slows the process of discovery, but it also forces the spending of public and private monies without any scientific basis for justifying the expenditures.

Surveys conducted by the Association of American Medical Colleges—National Association for Biomedical Research and the Pharmaceutical Manufacturers Association reveal that the cost of the proposed rules on regulated institutions will require a capital investment of at least $1.6 billion plus

an additional $450 million annually to maintain compliance. This is more than double the cost estimates given by APHIS.

The suggestion by APHIS that "increased costs of compliance will be passed from the regulated industry to consumers who purchase their goods and services." (*Federal Register,* Vol. 54, No. 49, March 15, 1989, page 10930) not only is unrealistic, but it displays an apparent lack of knowledge by the agency as to the established protocol for the conduct of research at institutions of higher learning.

Moreover, the agency's claim that current funding for biomedical research suggests that these regulations would not cause research establishments to abandon the use of animals is further evidence that APHIS does not understand the process for funding research. Funds made available for research, by and large, are for fixed costs and institutional overhead expenses with virtually nothing being available for either construction or renovation.

Inasmuch as there are no provisions in the law for financing these additional costs, the ultimate result for many institutions will be major cutbacks in ongoing and future research programs or, for some, the elimination of all research and teaching involving the need for live animal models.

As a means of mitigation of this exorbitant financial burden, the Society recommends that those animals obtained for acute experimentation be exempted from the proposed rules insofar as the rules relate to housing, exercise, and psychological well-being; thus eliminating for most research institutions a considerable capital expense of having to provide larger size pens, runs, and facilities for the gang-housing of animals. Among the reasons for such an exemption is that animals obtained for acute experiments, such as random source dogs, are not maintained for an extended period of time. Furthermore, they should not be gang-housed as such animals frequently react unfavorably to the other animals and instigate fighting, a consequence of which is stress on the animal population.

This exemption is consistent with the Society's comments on Parts I and II wherein it recommended that research involving non-survival surgery of fully anesthetized animals be exempt from the proposed rules. However, no inference should be made that the recommendations imply an acceptance by the Society of design standards for laboratory animals to be used in long-term projects.

As stated in the Society's earlier letter there is considerable concern about the extent to which the proposed rules continue to differ from the laboratory animal welfare policies and guidelines of the Public Health Service. Such differences only can lead to increased costs for both federal agencies and research institutions; confusion for the scientists and the animal care and use committees; and interference with the efficient conduct of research, none of which leads to improving the welfare of laboratory animals.

The Society also believes the promulgation of design standards based on an unsubstantiated consensus of APHIS veterinarians (*Federal Register,* Vol. 54, No. 49, March 15, 1989, page 10905) rather than scientific data is not only unacceptable as well as counterproductive to research, but it also is indefensible and inexcusable. Laboratory animal welfare assurance will always rest with the principal investigator and attending veterinarian and regulations must allow for their judgments. Laboratory animal welfare can not be assured by centralized procedures based solely on bureaucratic consensus.

In addition to the concerns cited above, the Society has the following specific recommendations:

Ventilation [Subpart A, 3.2 (b) and 3.76 (b)]. It is not possible in many parts of the nation to meet an absolute requirement for maintaining relative humidity within the limits prescribed. To be consistent with the Public Health Service policy, the Society recommends placing the responsibility with the institution to control relative humidity that meets the needs of the species being housed.

Lighting [Subpart A, 3.2 (c) and 3.76 (c)]. The Society recommends the deletion of the requirement for full spectrum lighting, replacing it with the Public Health Service's statment that "Lighting should be uniformly diffused through the animal facilities and provide sufficient illumination to aid in maintaining good housekeeping practices, adequate inspections of animals, safe working conditions for personnel, and the well-being of the animals." Despite manufacturers claims for full-spectrum lights, there appears to be no basis of benefit in laboratory animal welfare against which its high costs can be measured or justified.

Duration and extension [Subpart A, 3.6 (d) (5)]. A maximum of two years with the possibility of a one-year variance for complying with space requirements is too short of a time period for both public and private institutions to raise capital funds and to complete planning, design, and construction, should a major outlay of money be required. It takes a minimum of two years or more in most state general assemblies to secure capital fund appropriations for state-supported institutions and a similar time period for private institutions to conduct successful fund raising programs. The Society recommends that the variance be commensurate with a reasonable time period for raising the needed funds and completing the required construction.

Exercise and socialization for dogs [Subpart A, 3.7]. It is the Society's recommendation that this section be deleted inasmuch as APHIS admits that the proposed requirements for exercise of dogs was determined by consensus without scientific basis. To promulgate rules by an in-house consensus—rules that will require institutions to spend more than a billion dollars to achieve compliance—should be evidence enough that the section must be suspended until a scientific study for exercise and socialization of dogs has been completed.

The Society suggests that the scientific literature on exercise of dogs be reviewed, including a 1986 publication, "Laboratory Animal Husbandry: Ethology, Welfare, and Experimental Variables," by Michael W. Fox, the scientific director of the Humane Society of the United States, wherein it is stated:

> "Many people claim that exercise is important for animals, but animals in nature that are well-fed, warm, not afraid of predation, and not sexually frustrated do not exercise. Exercise, per se, is an anthropomorphic concept, an unbiological activity at variance with the law of conservation of energy. . . . No drive to exercise has been recognized by ethologists, although the basic drives to be active and explore may be antropocentrically misinterpreted as exercise."

A 1987 study published in the *American Journal of Veterinary Research* tells of the activity and behavior patterns observed during the exercise period of purpose-bred beagle dogs housed individually or in groups and run housing. The animals from all groups showed little inclination to increase their physical activity, but fighting among group-exercised animals was noted at the third week of exercise.

In essence, exercise, per se, is neither natural nor beneficial for dogs in some cases could prove to be detrimental.

While scientific information on exercise for dogs is limited, what has been published is consistent between behavioral and biological practitioners. The Society urges that APHIS reevaluate section 3.7 and direct the responsibility for exercise of dogs to the principal investigator and the attending veterinarian at the research institution, as directed in Section 13 of the Animal Wealth Act.

Additional requirements for research facilities [Subpart D, 3.81]. Like the section concerned with exercise for dogs, the Society also believes for this section further study is required for the purpose of gathering scientific data regarding the psychological well-being of non-human primates.

The Society acknowledges that the psychological well-being of an animal is a necessary element for humane care and also recognizes that it is difficult at best to define psychological in humans, much less defining it for non-human primates. Because there is a broad diversity in behavioral characteristics, not the least of which are related to species and age, it is most inappropriate to promulgate centralized regulatory definitions for the psychological well-being of non-human primates.

The recommendation of the Society is that the psychological well-being of non-human primates be the responsibility of the principal investigator and the attending veterinarian and that APHIS commission studies on pychological and behavioral stress in animals.

The American Physiological Society appreciates the opportunity to express the concerns of the nation's physiologists regarding the proposed rules for the implementation of the 1985 amendments to the Animal Welfare Act. The Society also is prepared to assist the the Animal and Plant Health Inspection Service with expertise from its membership for studies relating to the exercise and socialization of dogs and the psychological well-being of non-human primates.

Sincerely,

Vernon S. Bishop, PhD
President

The way of an investigator has changed.

We have passed through an era of "blessedness" when support of research was unquestioned as providing a source of betterment and progress.

We have faced with fragmentation of disciplines to subdisciplines.

We are increasingly aware that we can no longer liver in an ivory tower and insulate ourselves from political, economic and social pressures.

We must accept the inevitability of change in university structure from an aristocratic one to a demoncratic form involving the student and faculty community inits decisions.

Somehow, we must change the connotation of the conjunction between teaching and research to teaching with research so that the public and government recognize their inseparable nature in the university.

Loren D. Carlson

(Excerpt from Past President's Address, *Physiologist* 12: 425–432, 1969)

APS/ASPET '88
"Growth, Development and Aging"

A Summary of Selected Symposia From Meeting Held October 9–13, 1988, in Montreal
(Supported in part by AG-07924)

Symposium: Nutritional and Physiological Approaches to the Study of Aging

Chairman's Introduction

R. J. M. McCarter, University of Texas Health Science Center, San Antonio

There is growing interest in uncovering ways to retard the aging processes. This stems from both the desire to understand the primary aging processes and the practical needs of geriatric medicine. Nutritional manipulations are believed to be prime candidates in this regard, but only food restriction in rodents has clearly been shown to retard aging. It seems likely that learning the mechanisms by which food restriction retards the aging processes will provide insight into the nature of the primary aging processes as well as providing a data base for developing interventions of human aging. To this end the influence of food restriction on the rate of aging, gene expression, cellular function, and metabolic rate are discussed as well as potential mechanisms by which these effects are produced.

Proposal of Cellular Mechanisms for Food Restriction

Byung Pal Yu, University of Texas Health Science Center, San Antonio

The general lack of experimental data regarding the fundamental nature of aging poses methodological problems in finding a way to explore aging processes. Food restriction has found its place as the most effective and consistent means for slowing aging processes in a wide variety of organisms. However, the molecular mechanisms underlying such remarkable actions are still elusive, and the identification of factors and elucidation of processes responsible for the action of food restriction are acutely needed.

The most outstanding features of food restriction are the breadth of its efficacy and the impacts that are detectable almost ubiquitously in food-restricted organisms. A close examination of these unique features of food restriction may lead to explanations of the cellular mechanisms common to its diversified actoins.

Of several hypotheses proposed for the action of food restriction, the free-radical–induced lipoperoxidative membrane damage hypothesis is of particular interest because it can explain most of the characteristics of aging processes. Further support has been accumulated for the concept that food restriction modulates free-radical metabolism. Recently, we obtained evidence (Oxygen Radicals *Biol. Med.* 49: 1067, 1988) suggesting modulatory action of food restriction on age-related membrane alterations, cytosolic antioxidant system, and the cellular eliminating process of malondialdehyde.

Taking into consideration these data and others, "Cellular Homeostasis Hypothesis" is proposed. This hypothesis provides the integrated role of food restriction in maintenance of cellular homeostasis. This is accomplished by regulating free-radical reactions, enhancing selected antioxidant defense components, and expediting removal of deleterious metabolic by-products. If one defines that aging processes are associated with a loss of control over cellular homeostasis responses, this model can offer a mechanism for the diversified action of food restriction on retardation of aging processes, reduction of disease incidences, and life extension.

Alteration of Gene Expression by Caloric Restriction in Rats

Arlan Richardson. Illinois State University, Normal

Dietary restriction (underfeeding, not malnutrition) is the only experimental manipulation that has been shown to consistently increase the longevity of mammals. Although research during the past decade has shown that dietary restriction alters a variety of disease processes and increases the survival of laboratory rodents, the mechanism responsible for the increase in longevity is currently unknown. Our laboratory is studying the hypothesis that dietary restriction exerts its effect on the aging process through changes in gene expression, either at the level of translation or transcription. In a series of experiments, it was found that the protein synthetic activity of liver, kidney, and lymphocytes was significantly higher in tissues obtained from rats maintained on a restricted diet. More recently, it was shown that the genetic expression of α-2u-globulin was modulated by dietary restriction. The synthesis, mRNA levels, and nuclear transcription of α-2u-globulin by liver tissue from old rats fed a restricted diet was two- to threefold higher than was the expression observed in liver tissue from rats fed ad libitum. Subsequent studies have shown that the mRNA levels of a variety of genes is modulated by dietary restriction. Preliminary evidence indicates that UV-induced DNA repair by hepatocytes and kidney cells is higher in rats fed a restricted diet. Thus, dietary restriction not only alters gene expression at both the translational and transcriptional levels but also appears to preserve the structural integrity of DNA.

Cellular Changes Produced by Dietary Restriction

Hildegard E. Enesco, Department of Biology, Concordia University, Montreal, Canada

Cellular changes that occur in normal in vivo mammalian aging include increases in chromosome aberations, lipofuscin, and polyploidy and decreases in nuclear size, cell size, and cell number. At the organelle level, age-related cellular changes include increases in smooth endoplasmic reticulum and in lysosomes and a decrease in the number of mitochondria.

In my studies, dietary restriction was imposed by means of protein restriction; Swiss albino mice were maintained on control (26% protein) and restricted (4% protein) diets produced by Teklad, Madison, Wisconsin. Aging changes were followed for 20 months for some of the cellular parameters listed. Protein restriction was found to slow the aging changes in several of these cytological parameters.

Lipofuscin increase in the brain was significantly slowed by protein restriction. The increase in liver polyploidy levels observed in liver in normal aging was also significantly slowed by protein restriction. Dietary protein restriction resulted in a significant decrease in cell number and in cell size in expanding cell populations such as liver and kidney but did not affect cell number or cell size in static cell populations such as brain and heart.

Metabolic Rate and Aging: The Interplay of Nutrition, Metabolic Rate and the Aging Process

Roger McCarter, Department of Physiology, University of Texas Health Science Center, San Antonio

It has long been held that metabolic rate plays a key role in aging processes. There is also much evidence that nutrition markedly influences aging. This presentation examines the hypothesis that the interplay between nutrition and metabolic rate provides the basis for the effect of nutrition on aging processes.

Early work showed that, in general, species having a high metabolic rate per unit of metabolic mass have a shorter life expectancy than do species having a lower rate of metabolism. These data, together with studies indicating a similar life-time caloric energy expenditure of animals having a wide range of life spans, led to the formulation of the Rate of Living theory of aging of Pearl and Rubner. Although considerable evidence supporting this theory has been obtained for poikolothermic animals, studies in homeothermic animals have produced equivocal data.

The effect of food restriction in retarding aging in laboratory rodents is now well established, but the mechanism of action is not understood. One possibility is that food restriction prolongs life by decreasing the metabolic rate, since it is well established that restriction of food intake causes a decrease in metabolic rate per unit of metabolic mass. Sacher first suggested this hypothesis, but life-time food consumption data in rats argued against this. Studies in our laboratory directly measuring metabolic rate of rats 24 hours per day under usual living conditions have demonstrated, however, that the hypothesis is not correct; i.e., the metabolic rate per unit metabolic mass of food-restricted rats declined significantly after initiation of restriction, but this decline was transient. For the major fraction of the life span of these rats, the metabolic rates of food-restricted rats were not less than those of rats fed ad libitum.

Other data suggest that the action of food restriction on longevity should be viewed not on a unit tissue mass basis but rather on a per-animal basis (Masoro, E. J., *J. Gerontol.* 43: B61, 1988). If metabolic rate is viewed in this way, then both ad libitum–fed and restricted rats exhibit similar age-related variation, but the restricted rats operate at a lower set point or metabolic level. The interplay of nutrition and metabolic rate may therefore be viewed as affecting aging processes at the level of the entire organisms rather than on a unit tissue mass basis.

Symposium: Age-Related Changes in Excitation-Contraction Coupling Mechanisms in the Heart

Chairman's Summary

E. G. Lakatta, Gerontology Research Center, NIA, Baltimore, MD

This symposium educated our constituents regarding new perspectives from research that focuses on mechanisms of cardiac excitation-contraction and specifically on how age affects these mechanisms. Traditionally, most cardiac physiologists have studied the heart at a single point on a broad spectrum; i.e., they have used the most accessible animal model or human volunteer, usually of just postmaturational age. The symposium focused on age-associated changes that occur during the first few days after birth, throughout maturation, and into senescence. The symposium consisted of experts in biochemistry, morphology, electrophysiology, and physiology in an attempt to allow an integrated view of how changes in sarcolemmal ion transport, of sarcoplasmic reticulum (SR) development and function, and of the myofilaments interact to alter myocardial of cell function.

The initial presentation by Dr. Bers demonstrated that ontogeny (within rat) recapitulates phylogeny (rat vs. rabbit) regarding the functional aspects of cardiac muscle for rat and rabbits.

Development and Species Variation in Excitation-Contraction Coupling in Cardiac Muscle

D. M. Bers, University of California, Riverside

Based on experiments using ryanodine and caffeine to inhibit normal SR function, it has been suggested that there is substantial variation among cardiac tissues in the relative importance of SR Ca^{2+} release (compared with Ca^{2+} influx) in the activation of contraction. This variation is apparent developmentally (newborn vs. adult rat), regionally (rabbit atrium vs. ventricle), and among different mammalian species. The adult rat ventricle seems to be more dependent on SR Ca^{2+} release than is the newborn rat ventricle or adult rabbit ventricle (which exhibit similar physiological behavior). The difference in Ca^{2+} regulation in rat versus rabbit ventricle using rapid cooling contractures to assess SR Ca^{2+} content, extracellular double-barreled Ca^{2+} microelectrodes to assess transsarcolemmal Ca^{2+} fluxes, and Na-selective microelectrodes to measure intracellular Na activity (aNa_i) were examined. Rabbit ventricular SR and cells lose Ca^{2+} during rest (at a rate that appears to depend on the Na gradient) and gain Ca^{2+} on resumption of stimulation. Rat ventricular SR and cells gain Ca^{2+} during rest and lose Ca^{2+} on resumption of stimulation. Indeed individual steady-state contractions in the rat are associated with net Ca^{2+} extrusion, whereas in rabbit there is net Ca^{2+} uptake during the twitch.

These fundamental differences in Ca^{2+} fluxes undoubtedly underlie the well-known functional differences between these tissues (e.g., force-frequency relationship) and can be explained by *1*) the higher aNa_i measured in rat ventricle (12.7 ± 0.6 mM) than in rabbit ventricle (7.2 ± 0.5 mM), *2*) the markedly shorter action potential in the rat ventricle, and *3*) consideration of Ca^{2+} movements via Na/Ca exchange. That is, the higher aNa_i in rat favors Ca^{2+} entry at rest via Na/Ca exchange and the short action potential of the rat produces a negative membrane potential at the time $[Ca]_i$ is high, which favors extrusion via the Na/Ca exchanger during the twitch. The long plateau in the rabbit (during the time $[Ca]_i$ is high) prevents this Ca^{2+} extrusion via Na/Ca exchange.

It was concluded that the higher aNa_i and short action potential in rat ventricle explain many of the functional differences observed between this tissue and both adult rabbit and newborn rat ventricle.

The studies suggest that changes in cardiac muscle functon during development are linked to changes in the role played by the SR in excitation-contracton coupling. Dr. Jarmakani's presentation further developed this theme and explored developmental changes in sarcolemmal function as well. Dr. Mahony then described developmental changes in populations of SR isolated from sheep in which Ca^{2+} pump and Ca^{2+} release channel activity could be probed.

Developmental Changes in Cardiac Contractility and Their Relation to Sarcolemmal Ca^{2+} Flux and SR Ca^{2+} Release

J. M. Jarmakani, UCLA Medical Center

The neonatal myocardium develops less force than does the adult myocardium. In addition the inotropic effects of Ca^{2+} and catecholamine and cardiac glycosides in the newborn heart are greater than in the adult. This presentation described the developmental changes in the function of both the sarcolemma and SR that might explain the developmental changes in cardiac contractility. In the physiological preparation perfused with K-H solution at various Ca^{2+} concentration ($[Ca^{2+}]_o$), maximal contractility was achieved at $[Ca^{2+}]_o$ of 30 mm in the newborn and 7.5 mm in the adult, and the values in the newborn were one-half the values in the adult. The 1/2 maximal tension and $-dT/dt$ (max) (Km value) in the newborn (3.2 ± 0.11) were two times the values in the adult (1.40 ± 0.21). Total tissue Ca^{2+} as well as intracellular Ca^{2+} ($[Ca^{2+}]_i$) in the single cells were significantly less in the newborn than in the adult. In vitro experiments showed that the yield of myofibrils as well as the maximal ATPase activity increased with age. This explained, in part, the higher maximal contractile force in the adult compared with the newborn.

Sarcolemmal vesicles were isolated by differential and sucrose gradient centrifugation. In the newborn, maximal Na/Ca exchange was 24.6 ± 1.1 nmol $Ca^{2+} \cdot mg^{-1} \cdot 1.5$ s. Passive Ca^{2+} efflux rate was 14.6 ± 2.2 nmol $Ca^{2+} \cdot mg^{-1} \cdot min^{-1}$, and Ca^{2+} binding was 69.4 ± 3.3 nmol Ca^{2+}/4 min. These values were not significantly different from the adult values. The effect of pH on Na/Ca exchange was similar in the newborn and adult. In the physiological preparation, the negative inotropic effect of verapamil and diltiazem (Ca^{2+} antagonists that reduces the slow inward current) in the newborn is significantly greater than in the adult, and this suggests that the newborn heart is more dependent on transsarcolemmal Ca^{2+} influx for contraction.

Sarcoplasmic reticulum isolation and Ca^{2+} uptake showed that the yield of the SR protein in the fetus (0.5 ± 0.06 mg/g muscle) and newborn (0.04 ± 0.10) were significantly less than in the adult (0.82 ± 0.08). Sarcoplasmic reticulum Ca^{2+} uptake per gram muscle in the fetus (0.6 μmol/g muscle) and newborn (2.0) were significantly less than in the adult (93.5 μmol/g). In the physiological preparation, ryanodine was used to inhibit SR Ca^{2+} uptake and release in the fetus, newborn, and adult rabbit hearts. The negative inotropic effect of ryanodine in the fetus [$-dT/dt$ (max) = 75 ± 5% control] and 3-day-old (978 ± 2% of control) was significantly less than in the 7-day newborn (58 ± 3%); the 7-day newborn value was significantly less than in the adult (44 ± 2% of control). In addition, ryanodine prevented the positive inotropism of staircase in the adult and only attenuated this effect in the newborn. The data indicate that *1*) Ca^{2+}-stimulated SR Ca^{2+} release increases with age in the rabbit and *2*) Ca^{2+} influx is the major source of contractile Ca^{2+} in the fetus and newborn while Ca^{2+} release from the SR is the major source of contractile Ca^{2+} in the adult.

Developmental Changes in Subpopulations of Cardiac SR

L. Mahony, University of Texas Southwestern Medical Center, Dallas

Developmental changes in myocardial function have been described by a number of investigators. To further define the cellular basis of these changes, SR vesicles enriched in either longitudinal or junctional SR were isolated from fetal and maternal sheep hearts. Measurements of marker enzyme activities in these SR preparations showed little contamination by sarcolemmal or mitochondrial membranes. Calcium uptake, Ca^{2+}-dependent ATPase activity, apparent Ca^{2+} pump coupling ratio, and concentration of acyl-phosphoprotein intermediate were all significantly decreased in the longitudinal SR vesicles from fetal hearts compared with values obtained in longitudinal vesicles from maternal hearts. The junctional SR vesicles from both fetal and maternal hearts showed a fourfold increase in Ca^{2+} uptake when ryanodine was added to the incubation media.

These observations confirmed that these preparations were indeed enriched in Ca^{2+} channels. Again, Ca^{2+} uptake was markedly decreased in the fetal vesicles. Interestingly, the ratio of Ca^{2+} channels (measured by [^{3}H] ryanodine binding) to Ca^{2+} pump was increased twofold in these same fetal vesicles. These data suggest substantial developmental changes in cardiac SR function. Inasmuch as Ca^{2+} uptake is significantly decreased in fetal SR vesicles, the ability of the immature heart to alter relaxation may be relatively limited.

Developmental aspect of Ca^{2+}-channel current that is activated by sarcolemmal depolarization and triggers SR Ca^{2+} release was discussed by Dr. Lederer. His studies suggest that the link between sarcolemmal Ca^{2+} channels and SR Ca^{2+} release channels is not fully formed at birth but develops after the immediate neonatal period.

Developmental Changes in the Calcium Current in Rat Heart: Implications for Excitation-Contraction Coupling

J. W. Lederer, University of Maryland, Baltimore

In the rat, developmental changes in excitation-contraction coupling appear to parallel developmental changes in the sarcolemmal Ca^{2+} current. These changes were examined with electrophysiological methods in isolated neonatal rat heart cells and in isolated adult rat heart cells. The plant alkaloid ryanodine was used to investigate these developmental changes. In skeletal muscle and in heart muscle, ryanodine has been shown recently by several groups to bind to a receptor that has been identified with two functions: *1*) it spans the space between the sarcolemmal and the SR, and *2*) it functions as an SR Ca^{2+} release channel. Ryanodine, on binding to its receptor, blocks the normal link between excitation and SR Ca^{2+} release. The application of ryanodine in adult heart cells was found to significantly alter the sarcolemmal Ca^{2+} current independent of changes in free $[Ca^{2+}]_i$ (controlled by intracellular EGTA or BAPTA) but produces virtually no change in the Ca^{2+} current in neonatal heart cells. Additionally the properties of the ryanodine-treated adult heart Ca^{2+} current appear to be very similar to those of the neonate. Ultrastructurally, the neonatal heart cells appear disorganized when compared with adult heart cells. These results suggested that the "spanning protein/SR Ca^{2+} release channel" complex (ryanodine receptor) may link the Ca^{2+} channel function to the SR function in adult rat heart cells, whereas in the neonatal heart those links have not yet been fully formed. These findings imply that the ryanodine receptor may function as a communication pathway between the sarcolemma and the SR that may be important in excitation-contraction coupling in heart.

Focus then shifted to the senescent heart, and an overview of changes that occur in various excitation-contraction coupling mechanisms was presented by Dr. Lakatta. A major point was that the prolonged contraction and the underlying cellular mechanisms that cause it could be interpreted as adaptive rather than degenerative.

Excitation-Contraction Alterations in Cardiac Muscle that Occur in Senescence

E. G. Lakatta, Gerontology Research Center, NIA, Baltimore, MD

Most information of how advanced age affects mechanisms that govern the cardiac contraction comes from studies in the rat model. Contractile force production of isolated rat cardiac muscle, at low

rates of stimulation at least, is preserved in advanced age. While there is no clear-cut indication that passive stiffness in isolated cardiac muscle is increased with aging, the dynamic stiffness measured during the contraction increases. The affinity of the myofibrils for Ca^{2+} is preserved in senescent muscle, and the increase in myoplasmic [Ca^{2+}] after excitation is not age related. In the senescent cardiac muscle, contraction is prolonged, in part because the Ca^{2+} released into the myoplasm during systole is removed more slowly than in the muscle of younger hearts. A major cause of this is a reduced rate of Ca^{2+} sequestration by the SR. While the action potential duration is also longer in senescent than in younger cardiac muscle, its role in the prolonged contraction is less clear. The action-potential changes could reflect age-related changes in sarcolemmal ionic conductances or could be the result of the prolonged myoplasmic Ca^{2+} transient elicited by excitation. In the older heart, myosin isoenzyme shifts to slower forms and ATPase activity declines. These changes appear to underlie the observed decline in shortening velocity in isolated senescent muscle contraction in the isotonic mode. The reduced shortening velocity could also affect myofilament Ca^{2+} affinity, thereby prolonging activation, and also permits force development at a lower metabolic cost. These interrelated alterations in excitation-contraction mechanisms and myofibrillar biochemistry that accompany senescence can be construed as adaptive rather than degenerative in nature and serve to maintain the contractile requirements of the senescent heart as pump requiring a prolonged systolic force bearing capacity.

Evidence supporting the notion that the age-associated changes described are adaptive in nature stems from the observation that these changes do not occur independently of each other. Specifically, the pattern of changes in excitation-contraction coupling mechanisms that occurs with aging can be mimicked in younger animals by chronic experimental hypertension. At least one of these changes, the shift in the isomyosin form, is a change in genetic expression of protein synthesis, i.e., a pretranscriptional change. Whether the changes in the various organelle membrane functions described are due to changes in the expression of proteins that determine or modulate ion channel activity at the sarcolemma (prolonged action potential) or the SR pump (prolonged Ca^{2+} transient; decreases in SR Ca^{2+} transport rate) is presently unknown. However, it is tempting to speculate that because these changes do not occur in isolation of each other, they may all be directed from within the genome. This would require a "logic" within the genome that controls the simultaneous expression of multiple genes for cellular adaptation to occur. For aging and experimental hypertension, altered myocardial cell loading would be the macroscopic stimulus that signals this genetic "logic" to alter protein expression. The microscopic signal that transduces the signal is presently unknown but could be factors such as stretch or a change in cell ion gradients (Ca^{2+}, H^+) resulting from altered mechanical loading of cardiac cells.

Excessive thyroxine (T4) administration produces a pattern of change in these variables in the opposite direction of aging and experimental hypertension and can in large part reverse age-associated changes. Short-term T4 administration has been shown to reverse the age-associated changes in myosin isozyme expression and its biochemical myosin (Ca^{2+} ATPase activity) and functional (contraction time to reach duration) sequelae also.

The inotropic responses of isolated rat cardiac muscle to cardiac glycosides and to β-adrenergic stimulation are reduced in senescence. Finally, although the Wistar rat is prone to develop renal disease with aging, this has been shown to have no relationship to the altered β-adrenergic response or to the prolonged contraction.

The symposium concluded with Dr. Narayanan's presentation of his studies regarding changes in ATP-driven Ca^{2+} pumps that may explain in part the prolonged contraction in the senescent heart.

Age-Related Changes in ATP-Driven Calcium Pumps in Heart Muscle

N. Narayanan, University of Western Ontario, London

Prolonged duration of contraction is one of the most striking and well-documented effects of aging on the mechanical performance of cardiac muscle in a variety of species, including rat, guinea pig, dog, rabbit, and human. The prolongaton of cardiac contraction seen with aging is recognized to be due to an increase in both time to peak force and half-relaxation time. Conceivably, the duration of contraction may be determined to a significant extent by the duration of excitation-induced elevation of Ca^{2+} concentration in the muscle sarcoplasm. In the heart, contraction- and relaxation-related Ca^{2+} translocation rests mainly on the sarcotubular and sarcolemmal membrane systems. Age-related changes in the Ca^{2+} translocation function of these membranes can, therefore, contribute to the prolonged contraction duration observed in the aging myocardium. Evidence supporting this possibility emerged from studies that examined the effects of aging on ATP-energized Ca^{2+} transport (Ca^{2+} pump) activities of SR and sarcolemma from rat myocardium. Thus, it has been observed that in rat myocardium, moderate yet significant decline in the Ca^{2+} pump activity of SR is manifested as early as 12 months of age; further progressive deterioration of this membrane function follows aging, thereafter resulting in about 50% decline at the age of 24 months. Although an appreciable age-related increase in the Ca^{2+} pump activity of sarcolemma becomes evident late during adult aging, this is insufficient to compensate for the age-related decline in the SR Ca^{2+} pump activity. Consequently, the overall ability of the myocardial cell to sequester Ca^{2+} from the sarcoplasm via the ATP-driven Ca^{2+} pumps declines approximately 35%–40% during adult aging. No significant age-related Ca^{2+} differences could be observed in the Ca^{2+}-stimulated ATPase activities of SR and sarcolemma or in the apparent affinities of these membrane Ca^{2+} pumps for Ca^{2+}. These findings are consistent with the possibility that age-associated deterioration in the Ca^{2+} pump function of SR is a major factor underlying the prolongation of cardiac relaxation seen with aging. The age-associated impairment in SR Ca^{2+} transport activity may involve uncoupling of the energy transduction and ion translocation functions of this membrane Ca^{2+} pump.

Symposium: Age-Related Changes in Adrenergic Control of the Cardiovascular System

Age-Related Changes in the Structure and Responsiveness of the Heart and Vasculature to Adrenergic Agents

K. Rakusan, University of Ottawa

The rate of cardiac growth in humans is proportional to the rate of body mass. Consequently, relative heart weight in humans does not change considerably from birth to adulthood, and it increases significantly from 0.55% in middle age to 0.80% in centenarians. This increase in relative heart weight is probably due to a concomitant age-related increase in blood pressure and a moderate decrease in body weight in higher age groups. It is also accompanied by an increase in the diameter of cardiac myocytes, which is significantly correlated with both the blood pressure and age. Similar but less pronounced changes may be detected in all mammalian

species, even in the absence of an age-related increase in blood pressure. For instance, in the rat heart, moderate left ventricular hypertrophy is accompanied by a similar increase in the muscle cell volume. Variability in the muscle cell size increases with age, with a possibility of the cell loss in the senescent myocardium.

These changes are accompanied by a significant rarefaction of the coronary capillary bed that occurs in the aging heart as demonstrated by several authors in histometric studies. The functional capillary supply of the subepicardial capillaries was studied by cinemicrophotography of the beating heart in open-chest rats. The youngest age group was characterized not only by shorter intercapillary distances but also with higher degrees of capillary recruitment when normoxemic conditions were replaced by hypoxemia. These data are also supported by findings of decreased coronary blood flow and coronary reserve in isolated, perfused hearts of aging rats, rabbits, and guinea pigs.

Finally, combined effects of age and isoproterenol on the cardiac output and regional blood flow were studied in 5-, 12-, and 24-mo-old conscious male rats. The resting cardiovascular values did not change within the age range studied. After infusion of isoproterenol (0.2 μg/kg min), the heart rate and cardiac output increased considerably in the youngest group, while only smaller increases in heart rate and no significant changes in cardiac output were found in the oldest group. Similarly open blood flow increased after isoproterenol in all organs in the 5-mo-old group (including right and left ventricular blood flow). In contrast, infusion of the same dose of isoproterenol in the 24-mo-old animals did not elicit any significant changes in the regional blood flow. Thus the response to β-adrenergic stimulation is depressed with advancing age.

Effect of Age on Adrenergic Transmission at the Cardiac Neuroeffector Junction

J. Roberts, Medical College of Pennsylvania, Philadelphia

The effect of age on the capacity of the right cardiac sympathetic nerve to release norepinephrine (NE) into perfusion effluent (NE overflow) was studied in hearts isolated from male Fischer 344 rats at 6, 12, and 24 months of age. The hearts were perfused through an aortic cannula with Krebs-Ringer solution, and the cardiac sympathetic nerve was stimulated electrically with supramaximal voltage at frequencies of stimulation that produced 20%, 50%, or 80% of maximal NE overflow at each age. The content of NE in the perfusion effluent was measured by electrochemical detection after alumina extraction and high-performance liquid chromatography separation. The NE overflow was significantly lower in hearts of 12- and 24-mo-old animals compared with hearts from 6-mo-old animals at each frequency of stimulation. In addition the frequency of stimulation necessary to produce 50% or 80% of maximal NE overflow was significantly greater in heart preparations from both 12- and 24-mo-old animals compared with preparations from 6-mo-old animals.

Perfusion with cocaine (10^{-6} M) significantly increased the quantity of NE in the effluent after nerve stimulation only in hearts from 12- and 24-mo-old animals. Nevertheless, NE overflow remained significantly lower than that observed in hearts of 6-mo-old animals. The results suggest that the capacity of the cardiac sympathetic nerve to release NE is diminished in 12- and 24-mo-old animals. Furthermore, in these age groups an increase in neuronal uptake appears to reduce further the quantity of NE made available to the heart. These changes seem to occur by middle age and persist to senescence.

The density of β-adrenergic receptors in heart ventricles, as determined by the specific binding of ^{125}I-iodohydroxygenzylpindolol (IHYP), did not differ significantly in rats aged 6, 12, and 24 months. Also, no age-related difference was seen in the affinity of cardiac β-receptors for this antagonist radioligand. After chemical sympathectomy (with 6-hydroxydopamine hydrobromide), the maximal number of β-receptor sites was significantly elevated in all three age groups, indicating that aging does not compromise ability of the heart to invoke upregulation of β-adrenergic receptors.

Influence of Aging on β-Receptor Adenylate Cyclase System of the Heart

I. B. Abrass, Harborview Medical Center

Diminished capacity to respond to stress is one of the widely recognized functional deficits of the heart in aging humans as well as animals. Evidence from various studies has indicated that this impaired stress responsiveness is due at least in part to an age-related decline in the response of the heart to adrenergic stimuli. Thus the positive inotropic and chronotropic responses to sympathetic stimulation and infusion of β-adrenergic agonists have been shown to be significantly reduced in aged heart. Further diminished contractile response to catecholamines in cardiac muscle isolated from the senescent compared with the adult rat has been demonstrated, suggesting an age-related defect intrinsic to the myocardial tissue. Age-related alterations at the level of various components of the β-receptor adenylate cyclase system (i.e., the β-adrenergic receptor, adenylate cyclase catalytic unit, and the GTP binding regulatory protein, N_S) and cAMP-dependent protein kinases as well as their phosphoprotein substrates can, conceivably, contribute to impairment in adrenergic responses of the heart, because all of these components are thought to be involved in the translocation of adrenergic input to physiological response. Studies from several laboratories have shown striking age-related changes at the level of the β-receptor–adenylate cyclase system in rat myocardium. Whereas the density of the β-adrenergic receptors does not appear to be altered significantly in the aged heart, β-receptor–mediated stimulation of adenylate cyclase by catecholamine agonists and guanine nucleotides declines markedly with aging. This age-related decline in agonist activation of adenylate cyclase is also accompanied by a conspicuously reduced ability of guanine nucleotides to regulate β-receptor affinity for agonists. Further, β-receptor–independent activation of the cyclase by guanine nucleotides, NaF and forskolin, also declines significantly with aging. These findings suggest an age-associated deterioration in the functional integrity of myocardial β-receptor–linked adenylate cyclase system; this may contribute, at least in part, to the diminished adrenergic responsiveness of the heart in aging. The molecular basis of the age-related functional defect in β-receptor–cyclase system is yet to be established but may involve impaired interaction between the macromolecular components viz the β-receptor, guanine nucleotide regulating protein (N_S), and the adenylate cyclase catalytic unit.

Effect of Age on the Vascular Adrenergic Neuroeffector Junction

S. P. Duckles, University of California, Irvine

Little is known about the mechanism of changes in cardiovascular function with age, such as increase in blood pressure and levels of circulating plasma catecholamines and increased incidence of postural hypotension. Recent evidence indicates that vascular adrenergic responsiveness is remarkably well maintained with increasing age from maturity through senescence. In the Fisher 344 rat, vascular reactivity in vitro to adrenergic nerve stimulation and exogenous norepinephrine does not change with age from 6 to 27 months. This is true in both arteries and veins and occurs despite a decline with age in norepinephrine content in most arteries but not in veins. The ability of adrenergic nerves to accumulate norepinephrine is also not changed with age, as assessed by several techniques, including effect of cocaine on contractile responses and

measurement of accumulation and uptake of [^{3}H]norepinephrine. Vascular relaxation to β-adrenergic stimulation does decline in arteries, but this occurs before 6 months of age. In the rat jugular vein, responsiveness to β-adrenergic stimulation is constant from 3 to 27 months of age. Because many aspects of vascular adrenergic responsiveness remain stable with increasing age, the hypothesis that the ability of vascular smooth muscle to adapt to alterations in adrenergic nerve activity might become blunted in older animals has been tested. Denervation supersensitivity after 7 days treatment with reserpine has been measured in the tail artery from animals 6 or 20 months of age; however, the degree of denervation supersensitivity did not decline with age. Thus the ability to respond to stress is also maintained with advancing age. The current study focuses on a discrete aspect of blood pressure control in a species where atherosclerosis is not prominent. Alterations at other sites, such as baroreceptor sensing, central control, or ganglionic transmission could also be responsible for changes in cardiovascular homeostasis.

Effect of Aging on Adrenergic Responsiveness of the Vascular Smooth Muscle

B. B. Hoffman, Stanford University, Stanford, CA

In the blood vessels of several species, the ability of β-receptors to mediate smooth muscle relaxation declines with increasing age, although the mechanism is uncertain. This problem has been pursued in two systems, i.e., arteries from rats studied in vitro and human veins studied in vivo. In both the aorta and mesenteric artery from older rats there is a decline in smooth muscle relaxation induced by isoproterenol and the adenosine receptor agonist NECA. However, relaxation induced by forskolin and cAMP analogues is largely preserved. In addition, isoproterenol-induced cAMP accumulation is blunted in vessels from older rats. These findings suggest that the blunted cAMP accumulation may be the rate-limiting alteration that could explain the impaired response to β-agonists with increasing age. To test this possibility, the ability of isoproterenol to activate cAMP-dependent protein kinase was measured in vessels from older rats. These experiments demonstrated that the vessels from older rats had similar amounts of the kinase when compared with vessels from young rats; however, the ability of isoproterenol to activate the kinase was greatly impaired in the vessels from the older rats. These results support the hypothesis that the defect in the vessels from the older rats is a blunted cAMP response that is not sufficient to activate cAMP dependent kinase. Vascular responses in people have been examined with the dorsal hand vein technique that allows the construction of complete dose-response curves without the drug-inducing systemic effects. This method has demonstrated that there is impaired isoproterenol-induced venodilitation with increasing age. However, relaxation mediated by the nonspecific vasodilator nitroglycerin is intact with increasing age. Interestingly, venodilitation induced by PGE_1 is preserved in older individuals who do not respond to isoproterenol. Consequently, in people there appears to be great specificity in the loss in relaxation with increasing age.

Age-Related Changes in β-Adrenergic Modulation of Heart Function: Perspectives From Single Cells to Humans

E. G. Lakatta, Gerontology Research Center, NIA, Baltimore, MD

Overall cardiovascular performance is determined by the integrated function of multiple interdependent variables: *1*) coronary blood flow; *2*) heart rate; *3*) the load on the myocardium during shortening (afterload), which is multifactorial and depends not only on aortic pressure but also on other determinants of vascular impedance and on the instantaneous ventricular radius; *4*) the load or stretch on the myocardial fibers before excitation (preload or end-diastolic filling volume); and *5*) the level of the myocardial contractile state. The level of function of each of these factors is determined by basic cellular and extracellular biophysical mechanisms (e.g., Ca^{2+} fluxes), and each of these is subject to autonomic modulation. Abundant evidence indicates that the response of the cardiovascular system to β-adrenergic stimulation during exercise declines with age.

The average basal level of norepinephrine increases with advancing age in many but not all populations, and in response to stress, the average level increases to a greater extent in elderly as opposed to younger individuals.

In some elderly individuals, a high cardiac output during exercise as in younger individuals is maintained by a slower heart rate, a greater stroke volume, and increased end-diastolic and end-systolic volumes. This greater reliance on the Frank-Starling mechanism and lesser reliance on heart rate occurring in the presence of the exaggerated plasma catecholamine levels in elderly subjects during exercise are the same hemodynamic patterns that occur during exercise in the presence of β-adrenergic blockade.

Both the β-adrenergic relaxation of smooth muscle and the β-adrenergic stimulation to strengthen myocardial performance facilitate the ejection of blood from the heart. An age-related increase in characteristic aortic impedance as a result of either deficient β-adrenergic modulation of smooth muscle tone or structural changes that occur in the aorta and large vessels with aging could partially account for the exercise-induced reduction in end-systolic volume and the increase in ejection fraction compared with resting values in some elderly versus younger human subjects.

Evidence for a reduction in the effectiveness of β-adrenergic stimulation to relax vascular muscle comes from studies in isolated aortic muscle from young adult and senescent animals, which demonstrate a diminution in relaxation in response to β-adrenergic agonists but not in response to nonadrenergic relaxants. Thus a deficiency in arterial dilatation during exercise, in addition to structural changes that may occur within the large vessels with age, may contribute to an enhanced vascular impedance and may be implicated in the alterations in the ventricular ejection pattern in some elderly individuals.

Age-related changes in the effect of β-adrenergic stimulation on the myocardium have been demonstrated most extensively in the rat model. In isolated cardiac muscle or perfused myocardium from rats of advanced age, the β-adrenergic enhancement of the contractile state is diminished compared with that in muscle of myocardium from younger adult rats. However, the effect of catecholamines to abbreviate to contraction duration is not age related. More recent studies in individual cardiomyocytes show that the contractile response to norepinephrine is diminished as is the phosphorylation of Troponin I.

β-Adrenergic modulation of pacemaker cells in part accounts for the increase in heart rate during exercise. The effect of bolus infusions of β-adrenergic agonists has been measured in many studies to determine whether a diminished heart rate response is associated with advancing age. Results of such studies are clear-cut in demonstrating that the response of heart rate to isoproterenol declines with advancing age. In senescent compared with younger adult beagles, the maximum heart rate response to isoproterenol infusion is and remains diminished in the presence of full vagal blockade with atropine. In contrast, the maximum heart rate that could be elicited by external electrical pacing, which was far in excess of that elicited by infusion of isoproterenol, was not age related. Infusions of isoproterenol in intact rats have also produced a diminished increase in heart rate with age.

An age-associated decline in higher-affinity binding sites of leukocyte receptors has been observed in recent studies with radiolabeled agonists. A diminished agonist-induced stimulation of adenylate cyclase and heart rate has been found in the rat model. Because the deficit can be corrected by addition of guanine nucleotides, it has been suggested that a diminished coupling of the recep-

tor to the catalytic subunit of cyclase occurs with aging over this range in the rat. Age-related changes that are distal to the receptor-cyclase system are required to explain at least in part the age-associated reduction in β-adrenergic relaxation of aortic smooth muscle and the diminished myocardial contractile response to norepinephrine in senescent compared with young adult muscle.

In summary, when perspectives from studies that range from measurements of the stress response in intact humans to measurements of subcellular biochemistry in animal models are integrated, a diminished responsiveness to β-adrenergic modulation is among the most notable changes that occur in the cardiovascular system with advancing age. In contrast, α-adrenergic responsiveness, of the vasculature at least, appears to remain intact. It is noteworthy that a diminished effectiveness of some aspects of autonomic modulation has been demonstrated in many other body organs as well. The precise molecular mechanisms for the age effects remains to be explained (as do the precise mechanisms of catecholamine modulation of cell function per se), and these mechanisms need not be the same from one tissue to the next or from one age period to another within the same tissue.

Symposium: Cellular Mechanism in the Development of Respiratory Control

Chair: Jay P. Farber, University of Oklahoma, Norman

There is a considerable body of information regarding the organization and electrophysiological properties of medullary respiratory neurons in adult mammals; however, it has only been within the last few years that studies have been completed that begin to address this aspect of respiratory control in the immature animal. This symposium attempts to summarize recent data from newborn and fetal mammals and place at least some of this information within the context of respiratory pattern generation in adults. Topics include basic discharge patterns and changes in membrane potential of respiratory neurons during the respiratory cycle; effects on breathing of changes in the extracellular environment of respiratory neurons (e.g., ionic composition); and electrophysiological characterization of respiratory neurons in vitro.

Diethelm W. Richter (University of Heidelberg) provided an overview of cellular events underlying the mammalian respiratory cycle. With analyses of medullary neuronal membrane potentials, evidence was presented to support the concept of dividing the breath into an inspiratory, postinspiratory, and expiratory interval. The relationship of the postinspiratory period to apneas of different origins was discussed, as was the relationship between changes in breathing due to hypoxia and the postinspiratory period. Origin of apneas within central neuronal circuitry is of special interest because apneic events represent prominent disturbances to the breathing pattern, especially in premature infants. Prolongation of the postinspiratory phase, as judged by the membrane potential trajectories of the appropriate medullary neurons, is a prominent feature of some types of apneic events. Thus it may be particularly important to analyze the postinspiratory phase when assessing disturbances in breathing patterns that occur during the neonatal period.

Application of membrane potential analyses to respiratory neurons in newborns was provided by Edward E. Lawson (University of North Carolina at Chapel Hill). Anesthetized neonatal piglets were studied. Membrane potentials consistent with inspiratory, postinspiratory, and expiratory depolarization were obtained from different medullary cells. Thus the newborn of at least one species clearly demonstrates a postinspiratory interval. Further, when cells were hyperpolarized by chloride injection, reversal of potential occurred when hyperpolarization due to postsynaptic inhibition would normally occur. This finding suggests chloride-mediated inhibition in neonatal as well as adult animals. The presence of postinspiratory cells in the piglet confirms the possibility that disturbances of respiratory rhythm during the neonatal period can depend specifically on factors regulating the postinspiratory phase; this possibility is further suggested by the finding in piglets that depolarization of postinspiratory neurons is prolonged (with simultaneous inhibition of inspiratory and expiratory neurons) during apnea induced by either electrical stimulation of the superior laryngeal nerve or ammonia in the larynx.

The presentation by Teresa Trippenbach (McGill University) focused on changes in extracellular environment of medullary neurons during hypoxia and relationships of such changes to ventilatory responses accompanying hypoxia in anesthetized newborn and adult rabbits. Effects on K^+ were considered. In response to hypoxia, extracellular K^+ concentration increased as a two-stage process, first with a low slope and then with higher slope to a plateau. These changes were smaller in amplitude and took longer to accomplish in the newborn animals. Excitation of phrenic nerve activity was associated with the first stage of K^+ increase, while apnea or gasping was recorded after $[K^+]$ had risen to its plateau value. Nonetheless a specific extracellular concentration of K^+ could not be associated with a given breathing pattern, and other factors (e.g., status of reticular activating sytem) must contribute to hypoxic response. Possibly, the blunted changes of extracellular K^+ in newborns represent a protective adaptation to hypoxia.

With the particularly immature anesthetized marsupial (opossum) neonate, extracellularly recorded action potentials from respiration-related units were examined by Jay P. Farber (University of Oklahoma Health Sciences Center). For units associated with the very brief (ca. 100 ms) inspiration in young animals, there were very few action potentials. It was emphasized that such paucity of discharge would be inconsistent with the inspired breath being finely modulated through feedback loops (i.e., from airway receptors). Further, bulbospinal projections of respiration-related units were unmyelinated in animals up to about 60 days of age; the combination of slow conduction times in the unmyelinated nervous system, coupled with a very brief inspiratory duration, also makes effective feedback modulation unlikely. Many expiratory cells had virtually no discharge in the young opossum unless airway pressure was increased so as to activate expiratory muscles; such effects occurred much less often in adult animals. Thus many cells in the expiratory neural network of young opossums could not be responsible for generation of respiratory rhythm.

The status of respiratory neuronal discharge in the chronically instrumented sheep fetus was discussed by Semyon Ioffe (University of Manitoba). In the fetal sheep, breathing is linked to behavioral state. Respiratory movements are most prevalent in the sheep fetus during rapid eye movement (REM) sleep. In general, extracellular medullary recordings yielded respiration-related units that were similar in discharge characteristics to those observed in adult mammals. Stability of discharge patterns across breaths was analyzed and was found to differ widely among cells. A particularly interesting question is what happens to respiration-related units when the animal becomes apneic during non-REM sleep. An expiratory cell (obtained during REM sleep) was presented that had a phasic activity pattern during apnea. Cells could also be activated during apnea. This type of information strongly suggests that behavioral modulation of respiratory neurons needs to be considered within the context of development.

An in vitro approach to characterizing the development of medul-

lary neurons, with potential involvement in respiration, was provided by Gabriel G. Haddad (Yale University). With brain slices from rats and intracellular recording techniques, neurons in the ventral portion of the nucleus tractus solitarius (vNTS), as well as vagal and hypoglossal nuclei, were studied. For the vNTS region in adults, two types of cells could be characterized on the basis of discharge adaptation, delayed excitation, postburst hyperpolarization, postinhibitory rebound, and patterns of action potentials. Possible sources for ionic currents were discussed. In newborns, only one population of cells could be charcterized; these cells had slow-spike adaptation and lack of delayed excitation. Cells from the vagal motor nucleus showed strong adaptation and delayed excitation, whereas cells from the hypoglossal nucleus showed little adaptation and no delayed excitation in both newborns and adults. These results suggest that one component of maturation of respiratory control may be in the electrophysiological properties of individual neurons.

Presentations at this symposium were aimed at providing a basis for further exploration of the developing nervous system with respect to the regulation of breathing. Several different experimental approaches were used; these approaches were able to illustrate some differences and similarities in the neurophysiological basis for ventilatory pattern generation between the immature and adult mammal. Of equal importance was the introduction of some issues that need to be resolved if we hope to understand some special aspects of respiratory control in the newborn and fetus.

Symposium: Thermoregulation: Development and Decline With Age

Chairmen's Introduction

B. A. Horwitz, University of California, Davis, and D. Robertshaw, Cornell University, Ithaca, NY

As mammals age, their ability to respond to thermal stress first improves and then declines, the neonate and the older animal being particularly susceptible to adverse thermal environments. This symposium focused on current research related to the physiological mechanisms underlying alterations of thermal homeostatic mechanisms with age. A summary of each presentation follows.

Development of Thermoregulation in the Newborn

B. A. Horwitz, University of California, Davis

Genetic as well as environmental factors influence the ability of neonatal (as well as aged) mammals to regulate their body temperature. To illustrate the influence of genetic factors, one can compare the thermoregulatory ability of different species of rodents whose level of maturity differs significantly at birth (e.g., the hamster, born very immature; the guinea pig, born relatively mature; and the rat, falling somewhere in between). During the first 3 weeks postpartum, the ability of these neonates to generate heat in response to cold and in response to norepinephrine (the mediator of nonshivering thermogenesis in the neonate) differs considerably, with the animals born very immature (hamsters) being unable to significantly increase their metabolism during cold exposure, while those born more mature being able to generate increasing amounts of heat. These differences are parelleled by the ability of brown adipose tissue to generate heat. More subtle genetic influences on thermoregulatory ability can be observed in neonates of the same species. For example, neonatal Zucker rats homozygous for the fatty allele (fafa genotype) have an attenuated response to cold exposure compared with the homozygous lean pups (FaFa) even at 2 days of age, with the response of the heterozygote (Fafa) being in between [Moore et al. *Am. J. Physiol.* 249 (*Regulatory Integrative Comp. Physiol.* 18): R262, 1985]. In addition to the influence of intrinsic factors that are dictated by the genome, there are also external factors that affect the thermoregulatory ability of the neonate. Factors such as ambient temperature, macronutrient content of the diet, and general nutritional status can significantly alter the magnitude of the heat generating responses of newborn mammals. Thus, even though the ability to thermoregulate in the newborn proceeds according to a genetically determined sequence, the amplitude of the responses in this sequence are modulated by external influences.

Body Temperature Rhythms: Development and Aging

M. Kluger, University of Michigan, Ann Arbor

In human infants, a rhythm in body temperature is not observed until several weeks of age, and the amplitude of this rhythm does not reach the adult level until after 6 months postpartum (Reinberg and Smolensky, *Pharmacol. Ther.* 22: 425, 1983). Kittrell and Satinoff (*Physiol. Behav.* 38: 99, 1986) have shown that in rats, the adult rhythm in temperature does not appear until 30–40 days after birth. The face that the nighttime rise in temperature in the rat can be blocked by antipyretic drugs [Scales and Kluger, *Am. J. Physiol.* 253 (*Regulatory Integrative Comp. Physiol.* 22): R306, 1987] led to the hypothesis that prostaglandin synthesis is an important component of this circadian rise in temperature. In a subsequent series of experiments from Kluger and colleagues, it was shown that an intraperitoneal infusion of polymyxin B, an antibiotic that inactivates some endotoxin, led to an attenuated nighttime rise in body temperature but had no effect on the daytime body temperature. The interpretation of these data was that the presence of endotoxin (possibly originating in the gastrointestinal tract) influences the endogenous rhythm in body temperature. In support of this was the finding that oral administration of the nonabsorbable antibiotics streptomycin and bacitracin led to suppression of both the nighttime and the daytime body temperatures of rats. Further evaluation of the hypothesis that signals from the gastrointestinal tract influence body temperature has utilized germfree mice. Compared with conventionalized mice (i.e., those that were formerly germfree), germfree mice have a significantly lower body temperature during daytime and nighttime hours. When germfree mice were monocontaminated with *E. coli,* there was no increase in body temperature. Within three weeks of exposure to conventional mice, the formerly germfree mice developed the conventional circadian pattern of body temperature. These findings led to the suggestion that some signal from the gastrointestinal tract (probably endotoxin) provides a tonic stimulatory signal that influences the rhythm in body tem-

perature. Since endotoxin-induced fevers are thought to be the result of the production of endogenous pyrogens (e.g., interleukin-1, interleukin-6, tumor necrosis factor), it is possible that these mediators are involved in the maintenance of the normal adult rhythm in body temperature. In the newborn, the lack of a pronounced body temperature rhythm may be the result of the time necessary to establish the adult pattern of intestinal flora.

Cold-Induced Thermogenesis in the Aging Mammal and the Effects of Exercise Training

R. McDonald, J. S. Stern, and B. A. Horwitz, University of California, Davis

The hypothermia that develops in cold-exposed older humans also occurs in cold-exposed older rats. To evaluate the physiological mechanisms underlying this decreased ability to maintain homeothermy, a series of experiments were designed using cold-exposed (2–6 h at 6°C) Fischer (F344) male rats. These experiments demonstrated that older rats (24 mo) had lower brown fat and nonshivering thermogenic capacity and less effective heat conservation mechanisms than did younger animals. That is, a comparison of 24- versus 7-mo-old male rats indicated that during several hours at 6°C, the older animals had lower body temperatures, lower cold-induced rates of oxygen consumption (heat production), lower norepinephrine-induced rates of oxygen consumption, lower purine nucleotide binding to brown fat mitochondria (an in vitro index of brown fat thermogenic activity/capacity), but no decrease in lean body masses. Comparison of 24- to 12-mo-old rats demonstrated that both age groups had comparable rates of oxygen consumption during cold exposure, comparable levels of purine nucleotide binding to brown fat mitochondria, and no decrease in lean body mass. Nonetheless, the 24-mo-old male F344 rats became hypothermic during cold exposure, while the 12-mo-old rats did not. These findings indicate that the 24-mo-old rats not only had attenuated nonshivering heat production (when compared with their 7-mo-old counterpart) but also were unable to conserve heat as well as the younger animals (7 or 12 mo old).

This decreased ability of the older rats to maintain homeothermy during cold exposure is influenced by extrinsic and by intrinsic (genetic) factors. An example of the forst is physical activity. Exercise training (treadmill running 5 days/wk for 6 mo) prevented the hypothermia from developing in the cold-exposed 24-mo-old rats. This protective effect was associated with increased cold-induced heat production, presumably from shivering because brown fat thermogenic activity/capacity was not affected—as indicated by unaltered levels of purine nucleotide binding to brown fat mitochondria and unaltered levels of brown fat bloot flow (an in vivo index of brown fat thermogenesis). That genetic factors may also modulate the ability of older rats to maintain body temperature is indicated by two findings. *1*) Sedentary 24-mo-old male Osborne Mendel rats did not become hypothermic during cold exposure while their F344 counterparts did. The fact that both groups exhibited comparable cold-induced rates of oxygen consumption suggests differences in the ability of the two strains to conserve heat. *2*) Older (24- and 27-mo-old) female F344 rats are better able to maintain their body temperature during cold exposure than are comparably aged males.

Taken together, these data indicate that the older rats' loss of thermogenic capacitity is not continuous with age and that this loss is influenced by gender, strain, and level of physical activity.

Neurochemical Changes Related to Thermoregulation During Development and Aging

R. D. Myers, East Carolina School of Medicine, Greenville, NC

Monoamine neurotransmitters in the anterior hypothalamic, preoptic area are thought to be involved in the physiological control mechanisms for both heat gain and heat dissipation. In many developing neonatal mammals, thermoregulatory responses for the defense against challenges in ambient temperature are not fully intact postpartum, presumably because the function of monoaminergic nerve cells is not yet intact. Conversely, it is clear that with advancing age, serotonin- and catecholamine-containing neurons in infracortical structures lose their synaptic reactivity. Pharmacological studies reveal that the age-related inability to cope with a warm or a cold shift in ambient temperature is linked to a partial dysfunction in central dopaminergic and/or noradrenergic pathways. Further febrile reaction to endotoxin is blunted in the aged animals. However, such incapacitation does not appear to be due to a generalized disablement of neuronal systems with advancing age. For example, the putative endogenous antipyretic, α-melanocyte-stimulating hormone, produces a significantly greater hypothermia in the aged rabbit than in the younger animals. Moreover, β-endorphin given centrally to the monkey produces a more intense hyperthermic response in the older animal compared with the young adult. Taken together, therefore, these observations suggest that *1*) certain specific telencephalic-diencephalic mechanisms that underlie the processes for both thermogenesis and heat loss are intact in the aged animal, and *2*) other neuronal elements such as monoaminergic systems are partially incapacitated with increasing age and would require greater receptor activation for functionally adequate thermoregulatory responses.

Heat Stroke in Humans: A Problem of the Elderly

D. Robertshaw, Cornell University, Ithaca, NY

Epidemiological evidence clearly suggests that the elderly are at risk during heat waves and during such events as the traditional Islamic 7-day pilgrimage at Mecca, Saudi Arabia. The main risk factor is a decline in the physiological capability to lose heat, with other factors often exacerbating this deficit. The site of the defective thermal regulation of the elderly has not been established. Evidence has accumulated that both the affector and the effector components of the thermoregulatory reflex are deficient. Thus older people are less able to discriminate temperature differences and show incomplete vasomotor and sudomotor responses to heat. This does not exclude a defect in the integrating role of the central nervous system. Additional factors that predispose to heat-related illnesses and may reflect a decline in autonomic function generally are dehydration and poor cardiovascular control especially when coupled with poor physical conditioning. Diseases such as hypertension, diabetes mellitus, and hyperthyroidism, especially when they are associated with obesity, are other predisposing factors. The role of physical conditioning appears to be very important in offsetting the decline in thermoregulatory function with age.

Conclusions

This symposium has illustrated some of the complex and diverse factors that must be considered when examining the development and decline of thermoregulation (as well as other physiological processes) with age. In the neonate, the temporal pattern of the development of effector mechanisms for maintaining homeothermy is markedly influenced by genetic endowment as is the magnitude of the animal's response to thermal perturbations. Superimposed on genetic factors are the effects of a variety of external conditions that modulate the magnitude of the neonate's thermoregulatory responses. The same phenomenon occurs in older animals, where their ability to maintain body temperature outside of the thermoneutral zone has been shown to be influenced by gender and level of physical conditioning. The mechanisms underlying these changes appear to involve central as well as peripheral elements and clearly require further definition.

Symposium: Changes in Receptor Responses and Neurotransmitters With Age

Modulation of Gene Activity During Aging in the Brain

Caleb E. Finch, University of Southern California, Los Angeles

A new approach to understanding the neurodegenerative diseases of aging focuses on modulation of gene activity in brain cells. By morphological and histochemical criteria, many neurons become atrophic during aging in the human and rodent brain. Examples include cholinergic neurons of the basal forebrain, dopaminergic neurons of the substantia nigra, and hippocampal pyramidal neurons. In contrast, neurons, of the dentate gyrus show increases of size and dendritic branching during aging and Alzheimer's disease. These contrasting examples indicate that very different functional outcomes can occur during aging. The premature onset in Down's syndrome of molecular changes resembling Alzheimer's disease (cerebrovascular and neuritic plaque amyloid; neurofibrillary tangles) indicates the potential importance of imbalanced expression of normal alleles in these processes; the Down's-related changes appear to demonstrate that the accumulations of amyloid and neurofibrillary tangles during Alzheimer's disease and the lesser but similar changes during normal aging do not require sequences that are not normally present. As a general working hypothesis, we are investigating the possibility that afferent signals influence gene activity in pathway-specific manners that lead some neurons to atrophy and others to grow during aging and neurological diseases of aging. Three rodent models are discussed: *1*) chronic 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra, *2*) effects of stress on the hippocampus, and *3*) effects of hippocampal deafferentation from entorhinal cortex lesions that damage the perforant pathway. Using recombinant genetic techniques to evaluate cell mRNA levels by in situ and blot hybridization with cRNA probes, we are establishing a number of new molecular approaches to analyzing change in gene expression that are models for changes during aging, Alzheimer's disease, and Parkinson's disease. In each case, we find changes in mRNA that are selective by brain region and cell type. The results suggest that many aspects of aging in neurons can be interpreted as changes that are not intrinsic to neurons but rather represent alterations that are secondary to external influences, such as mediated by hormones of stress or by altered inputs from afferent neurons. These findings may provide the basis for new interventions into age-related changes that depend on altered gene expression. As such, this direction of research extends to the domain of aging a central question of eukaryotic cell biology: the extent to which genomic totipotency is maintained in differentiated cells throughout the life span.

Anatomic Organization of the Monoamine and Neuropeptide Systems in Primate Neocortex: Implications for Aging

John H. Morrison, Scripps Clinic, Claremont, CA

Several monoamine and peptide neurotransmitter systems have been implicated in the pathology of Alzheimer's disease (AD). For example, both biochemical and anatomic data suggest that the noradrenergic, cholinergic, and serotonergic afferents to neocortex, as well as the interneurons containing somatostatin, degenerate or participate in neuritic plaque (NP) formation in AD. Such neurotransmitter-based data on AD pathology are difficult to interpret without detailed anatomic information on the cortical cells and circuits that normally contain the affected neurotransmitters. Data are presented concerning the regional and laminar organization of monoamine-containing afferents in primate neocortex and the degree to which the distribution patterns correlate with those of NP and neurofibrillary tangles (NFT) in AD. In addition, data on the distribution and synaptic circuitry of the somatostatin-containing cortical neurons are presented and discussed in reference to AD pathology. Formation of NP is likely to involve all of these systems; however, careful anatomic analyses of AD, normal human and nonhuman primate cortices suggest that this involvement may be secondary to the pathology of certain cortical pyramidal cells. Thus the involvement of monoamine- and somatostatin-containing systems in AD pathology may be linked to initial pathologic changes in their target site, the pyramidal cells of layers III and V, and not necessarily a primary pathologic event. However, given the anatomic organization and functional role of the monoamine projections, their degeneration would augment the loss of cohesive cortical processing that would result from the degeneration of cortical pyramidal cells.

Effects of Age on Amino Acids As Neurotransmitters

F. Mora, Central University Complutense, Madrid, Spain

The putative amino acids neurotransmitters, particularly glutamic and aspartic acid, are, at present, the focus of great interest. However, very few data have so far been reported on the relationship between amino acids and the normal process of aging.

The prefrontal cortex (PC) is an area of the brain of special interest for studies on aging because it is involved in cognitive, mnemonic, and emotional functions. Moreover, the PC contains higher levels of acidic amino acids than do other cortical areas, namely, parietal, occipital, and temporal areas. We have studied the possible changes induced by age on the endogenous levels of several amino acids, presumptively neurotransmitters in the PC.

The first study performed in tissue samples and gas-liquid chromatography analysis showed that aged rats (21–24 mo old) have a specific decrease in the levels of aspartic and glutamic acid in the medial prefrontal cortex (MPC) when compared with the levels in the same area of young rats (2–3 mo old). No changes were found in other subareas of the PC, such as sulcal (orbital) or dorsal cortex or temporal cortex. A follow-up study showed that this decrease found in the MPC seem to be age related and that it occurs in both medial prefrontal hemispheres. More recent studies using the push-pull in vivo technique and HPLC analysis of the perfusates in the MPC showed, however, no differences in glutamic or aspartic acid when young and aged rats are compared. These results could be interpreted as indicative that the decrease of acidic amino acids found in our studies with tissue analysis are due to a decrease of both the neurotransmitter and metabolic pools of neurons and possibly other neural elements present in the MPC.

Recently we have investigated in young and aged rats the interactions of acidic amino acids with other neurotransmitters present in the MPC such as dopamine, substance P, and CCK. The results obtained so far show the following. Dopamine produces a significant decrease in the levels of aspartic of both young and aged rats. Glutamate levels were unchanged in young and decreased in aged rats. Glycine and serine had a tendency toward increase in young rats and decrease in aged rats. On the contrary, CCK produced a selective increase of aspartic acid in young but not in aged rats. Glutamate was unaffected along with serine while glycine was significantly decreased in both young and aged rats. Substance P had no effects on the levels of amino acids in either group of rats.

These last results showed that an interaction exists between amino acids and other class of neurotransmitters and that this interaction could selectively be altered by aging in the rat. Further, these

studies provide the possibility for future experiments in which the function of different circuits in a specific area of the brain and its dysfunction in the aged brain can be revealed.

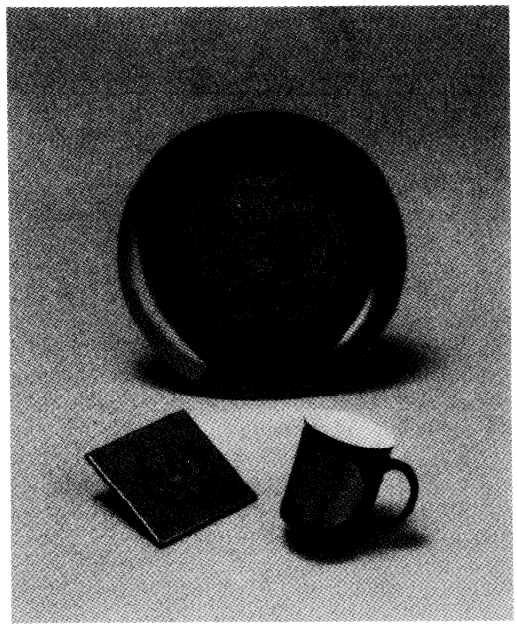
Reversal of Age-Related Transmitter Dysfunctions by Neural Transplants

T. J. Collier, J. E. Springer, and J. R. Sladek, Jr., University of Rochester School of Medicine, Rochester, NY

We have been studying the anatomical and functional correlates of intracerebral grafts of fetal neural tissue in three animal models of human aging and neurodegenerative disease. The first of these is the model of Parkinson's disease provided by MPTP treatment of African green monkeys. We have found that bilateral implantation of developing dopamine (DA) neurons into the striatum of debilitated monkeys yields marked recovery of motor function. This behavioral change is accompanied by identifiable clusters of grafted tyrosine hydroxylase–positive neurons, growth of neurites from these cells into the surrounding DA-depleted striatum, and local changes in levels of DA and its metabolites. Behavioral recovery appears to be lasting (< 1 yr) and is not obtained with sham procedures or implantation of non-DA tissue such as the cerebellum. Second, we have been studying norepinephrine (NE) supplementation in memory-deficient aged rats. A subpopulation of aged F344 rats exhibit profound deficits in acquisition and retention of spatial information. Marked recovery of learning and memory performance follows implantation of fetal locus coeruleus neurons into the ventricles or caudal cingulate cortex overlying the hippocampus. Again this behavioral change is accompanied by the presence of identifiable NE neuron grafts and is not obtained with implantation of cerebellar tissue. Finally, we have begun to study the effects of tissue implants as sources of trophic factors that may stimulate recovery of damaged or aging neurons in the host brain.

It has been shown that transection of the axons of cholinergic neurons projecting to the hippocampus leads to degeneration of these axotomized cells. This appears to be due in part to interruption of trophic support provided by transport of nerve growth factor (NGF). Addition of exogenous NGF rescues these damaged cells. In our studies, intraventricular implantation of NGF-rich tissue, male mouse submaxillary gland, produces a similar effect, rescuing axotomized cholinergic neurons, and in addition appears to stimulate sprouting of cholinergic fibers. Thus our studies indicate that the aged and damaged brain remains responsive to replacement or supplementation of neurotransmitters and trophic substances, yielding improved function.

American Physiological Society Centennial Collection



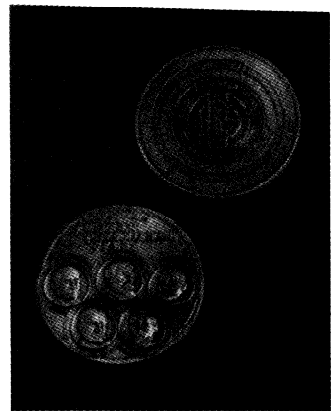
The Centennial Founders Set

The Centennial Founders Set is a limited production of ceramicware commemorating the 100th anniversary of the founding of the American Physiological Society. Each piece—plate, cup, and tile—is fired in a radiant cobalt blue porcelain and etched in 23-carat gold. The face of the 10-inch plate features a reproduction in gold of the Centennial portraits of the five founders and inscribed on the back is a brief history of APS. The tile features a gold reproduction of the Centennial Seal and the cup has both the founders' portraits and Centennial Seal embossed on the sides. A Founders Plate is to be donated to the White House Collection of Commemorative Plates in Washington, D.C.

The cost of the Centennial Founders Set is $45.00. Individual pieces are priced as follows: $35.00 for the plate; $10.00 for the cup; and $6.00 for the tile.

The Centennial Coffee Mug

Centennial Coffee Mug is a replica of the Founders Cup with the Centennial Seal imprinted in white on a radiant cobalt blue mug. The cost for the coffee mug is $7.50.



The Centennial Medallion

Centennial Medallion is a 2.5-inch bronze commemorative medallion that features the sculptured faces of the five founders on the front side and the Centennial Seal on the reverse side. The cost is $25.00 for each medallion.

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Temperature Biology of Animals

A. R. Cossins and K. Bowler
New York: Chapman and Hall (Methuen), 1987, 339 pp., illus., $57.50

Even a cursory examination of *Temperature Biology of Animals* tells us it deserves a long evening of careful reading; checking a list of items in the index provides evidence that it is up-to-date (Newton's Law of Cooling is not there, but Fourier is allowed five pages). Furthermore the text is readable as one would expect since the authors are British (their students read for a degree). The book includes the fundamentals of temperature biology but is also a comparative physiology.

Is another book on thermobiology justified? From 1967 to 1985 there were seven books on that topic, but all but two were multi-author reference books. Only one is recent and readable (again by English authors), but it is only about the temperature biology of man (Clark and Edholm, 1985). Yes, this new book is badly needed.

The first chapter covers the physics of thermal energy. The second chapter discusses the quantitation of the direct effect of temperature on cells; for example, the theoretical equations of rate-effects on biological processes are well explained and presented. There is some emphasis on temperature-independent processes, an important concept for biology students. The third chapter involves a distinction between ectothermic animals (body temperature determined by heat sources external to the body) and endothermic animals (body temperature determined by heat derived from cellular metabolism). The topics of thermal inertia and optimal body temperature are considered. Chapter 4 emphasizes the temperature regulation of birds and mammals. It proceeds like a typical chapter in a textbook of environmental physiology leading up to a climax in the discussion of set point. Chapter 5 gets down to the nitty-gritty of capacity and resistance adaptation and cellular mechanisms of adjustment. Chapter 6 is about thermal injury and thermal death. As you expect, we find here the cellular basis for thermal injury. Again, the authors boldly take the opportunity to relate the defined principles to animal distribution. Chapter 7 is a rare synthesis of temperature effects on reproduction. Several pages are devoted to a mathematical formulation of the rate of development with temperature. This is balanced by a discussion of temperature-sensitive stages and their ecological significance. As expected from these authors, the chapter ends with a modern discussion of temperature and gene expression.

There are a few faults: it is amusing that our English physiologists consider 1962 as "recent" (p. 62), but it is probably all right to think in a paleontological time scale. One stumbling block is the use of the terms "bradymetabolic" and "tachymetabolic." "Tachymetabolism" in the index refers to page 62 but there is no mention of this phenomenon on that page. Since both of these terms are new and perhaps inexact, they probably should be described with a reference as to their origin. One hopes that this will not be another case of new terms oozing into the literature. For example, there is a term "heterotherm" in the literature; if you ask Prosser where the term came from, he says that Morrison invented it; if you ask Morrison what the term means, he says that Prosser invented it. I have never yet found a reference as to origin or careful description of the term.

One portion of a chapter is entitled "Seasonal Effects Upon Acclimation." This appears to be a contradiction in terms because ordinarily when one studies seasonal effects we are dealing with acclimatization, not acclimation; the topic heading is confusing to students.

In summary, the authors have done an exquisite selection process; the volume was written for the whole-animal, organismic physiologist, but there is enough biomathematics to satisfy a quantitative mind. It is highly recommended for the specialist who will find it an excellent "annual review," and it might well be required reading for graduate students in biology and physiology.

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Neurobiology Molluscan Models

H. H. Boer, W. M. Geraerts, and J. Joosse (editors)
New York: North-Holland, 1987, 376 pp., illus., index, $59.00

Neurobiology Molluscan Models is the Proceedings of the Second Symposium on Molluscan Neurobiology, held at the Department of Zoology of the Free University, Amsterdam, The Netherlands, on August 18–22, 1986. The book contains 57 brief reports that are summaries of the presentations made at the meeting and, for the most part, of brief summaries of work previously published in peer-reviewed journals. The volume is dedicated to J. Lever, who is a recent retired senior lecturer at the Free University.

This book is organized into nine sections dealing with various subjects. The participants at the Symposium represented molluscan neurobiologists from most of the world, and this feature is a particularly attractive aspect of the book. For example, one presentation, entitled "Molluscan Neurobiology in the USSR," is an informative summary of the various types of studies performed in various laboratories in the USSR. While a large number of papers come from the host institution, there is good representation from both Eastern and Western Europe, Asia, and the Americas.

The first segment of the volume is concerned with identification of aminergic and peptidergic systems in molluscs and contains papers describing localization of serotonin, dopamine, CCK, FMRFamide, SCP, substance P, vasotocin, alpha bag cell peptide, opiates, and gonadotrpic hormones in the central nervous system of several different molluscs, including *Lymnaea, Aplysia, Helix,* and *Bulla.* Several of the papers document colocalization of peptides and/or amines, while others discuss actions in the different preparations. Four papers follow in a section entitled "Biosynthesis, Transport and Release of Neurochemical Messengers." Most of these papers focus on peptides.

The next sections are entitled "Central and Peripheral Actions of Neurochemical Messengers," "Molluscan Neurons in Applied Research," and "Receptors, Ion Channels, Intracellular Messengers." These 17 papers focus on receptors, both central and peripheral, and the effects of activation as well as the pharmacologic properties of the responses. Two particularly interesting studies document interactions between receptors (serotonin and dopamine) and different ionic currents (chloride and calcium).

The sixth section is an interesting collection of papers under the heading "Gene Coding, Structure, Purification and Evolutionary Aspects of Peptides." Although this field is clearly in its infancy as far as invertebrate models are concerned, the papers by Nagle et al. and Vreugdenhil et al. demonstrate that some real progress has been made in study of the genetic basis of neuropeptides in

invertebrates.

The final three sections of the book are entitled "Behavioral Physiology, Neuronal Integration," "Plasticity, Learning and Aging of the Nervous System," and "(Neuro)endocrine Control Mechanisms." The 20 papers in these sections are a good representation of recent (and some not so recent) activities of a number of good laboratories from around the world.

In many ways it is difficult to get very excited about this book. It has all of the pluses and minuses of proceedings: *1*) the papers are very brief; *2*) they usually summarize previously published work done several years earlier; and *3*) there is not enough detail to be very informative. There is, however, great value in these proceedings for the individual who is relatively new to the field and needs a single volume that indicates which laboratories are active in the study of molluscan neurons, as well as references to more detailed papers. The results in the book are somewhat dated in that the conference was held in 1986, the book published in 1987, and the review in 1989. The meeting appears to have been an exciting one and should have generated some good discussions that are unfortunately not included.

The book is published in paperback and is a particularly valuable source reference for students.

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Cellular and Molecular Basis of Cystic Fibrosis

Gianni Mastella and Paul Quinton (editors)
San Francisco, CA: San Francisco Press, 1987, 487 pp., illus., index, $40.00

Cellular and Molecular Basis of Cystic Fibrosis reports the proceedings of a symposium held in Verona, Italy in June 1987 devoted to reporting on the progress in basic research on cystic fibrosis (CF). More than 60 leading researchers from around the world were in attendance to report their latest research.

The scope of research covered is quite broad, covering advances in the genetics, biochemistry, and physiology of CF. The book begins with a chapter delineating some of the current clinical problems faced by CF patients and outlines recent progress in achieving solutions to these problems. Subsequent chapters focus on describing the results of the latest research in all the diverse areas relevant to the CF researcher. The book is conveniently divided into eight broad topics. The areas covered include genetics, electrolyte absorption, secretion, secretory products, cellular regulation, culture systems, and model systems. Each topic is covered by 6–10 research papers, each authored by some of the leading researchers in these fields. In most cases each chapter contains a comprehensive introduction to their research, reviewing current knowledge and problems encountered in each area. The papers are richly illustrated with figures and tables and all are well referenced. Each main topic contains at least one paper that could serve as a mini-review.

Although the physiological defect in CF appears to be a regulatory abnormality of epithelial electrolyte transport, especially of chloride, the biochemical defect remains unknown, and the search to establish its identity is intense. The symposium proceedings published in this book will be extremely valuable to the experienced CF researchers as well as those just entering the field as an excellent resource for the recent data, theory, and references.

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Progress in Molecular and Subcellular Biology—10

P. Jeanteur, Y. Kuchino, W. E. G. Muller, and P. L. Paine (editors)
New York: Springer-Verlag, 1988, 114 pp., $59.50

This volume consists of three chapters covering somewhat diverse but important areas of biology. The first article, by H. Stebbings, discusses the movement of macromolecules and organelles between nutritive cells and developing oocytes in meroistic ovaries. In some insects the nutritive tubes (cytoplasmic bridges) that connect the two cell types can be several millimeters in length and contain numerous microtubules. Dr. Stebbings has nicely summarized the unique structural features of the tubules, the nature of the materials that move through these structures (RNA, proteins, ribosomes, and mitochondria), the rates of translocation, and the involvement of microtubules in the process. Aside from their function in oogenesis, the nutrient tubules also represent a very useful model system for studying the general problem of cytoskeleton-associated translocation. Anyone interested in either of these areas should find this chapter worthwhile reading.

The second chapter, written by Paul Agutter, concerns the nucleocytoplasmic transport of mRNA and makes up about 70% of the book. In this chapter, Dr. Agutter develops the hypothesis that mRNA transport is a multistep, solid-state process that involves *1*) movement of mRNA along the nuclear matrix to the pore complexes, *2*) translocation through the pores, and *3*) migration within the cytoplasm along cytoskeletal elements. As background, the organization of the nuclear matrix, the structure and composition of the nuclear pores, the overall permeability properties of the nuclear envelope, and posttranscriptional processing of mRNA are discussed. In general, these discussions are quite helpful, although recent information on the composition of the pores is not included (specifically the finding that a novel class of O-linked glycoproteins are components of these structures), and the section on the matrix is more detailed and theoretical than seems necessary. Most of the research relating to the transport of mRNA has focused on the translocation step; in this regard, a comprehensive account of the ATP requirements, enzymatic reactions, and poly(A) involvement is provided. In addition, Dr. Agutter proposes a useful kinetic scheme for translocation and also discusses the possible role of mRNA transport in regulating gene expression. Overall, this review should serve as an excellent reference for both newcomers and experienced workers in the field.

The final chapter in this volume evaluates current hypotheses proffered to explain prebiotic evolution and the origin of life and was written by Klaus Dose. Dr. Dose starts by providing a brief but informative history of theories developed before 1924 and continues with a more detailed account of Oparin's views and the subsequent criticism of his "hot dilute soup" concept. The remainder of the article is concerned with the origin of genetic information. Dr. Dose points out that limited experimental data plus our ignorance of the environmental conditions during the prebiotic period make it impossible to draw any definitive conclusions; however, he suggests that the most likely scenario is the initial formation of protoproteins (including enzymes capable of catalyzing the polymerization of nucleotides) followed by the formation of nucleic acids.

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Advances in Comparative & Environmental Physiology

R. Gilles (editor-in-chief)
New York: Springer-Verlag, 1988, 252 pp., illus., index, $84.40

Sophisticated comparative physiological disciplines often arise to prominence slowly after the establishment of a given analytical technique that may have been instigated by the medical physiology community. A major reason for the latency period is that the breadth and width of comparative experiments requires investigating many taxonomic groups under varying and various environmental conditions. This book is the second in a series that indeed demonstrates that the time has come to recognize the respectable international status of several growing areas of comparative physiology.

Gilles' eclectic compilation covers hibernation, vapor absorption, nutrient transport, and heavy metal accumulation. The book's only apparent weakness is the assimilation of some unrelated topics. Its strength lies in the authoritative and definitive nature of the individual chapters, several of which provide a sort of membrane transport theme.

Ahearn's chapter on nutrient transport by marine invertebrate gut epithelium covers whole animals, cells, and isolated membranes. It is a thorough review of gut transport in four phyla, with a great deal of recent information from the author's own laboratory. This chapter is a prime example of how untapped knowledge concerning marine invertebrates has now been uncovered by employing epithelial membrane vesicle technology originally developed for mammalian physiology. Meticulous care is given to schematically explaining the anatomical, physiological, and biochemical basis for invertebrate nutrient transport experiments.

Studies of integumental transport in marine invertebrates have also advanced with the introduction of new technologies. As S. Wright points in this chapter concerning transport by marine invertebrates, the integument of molluscs, echinoderms, and annelids provides a significant means for absorbing dissolved organic nutrients. With a transparency afforded by extensive parallel experiences in the fields of invertebrate and mammalian transport, Wright reviews and explains the integumental mechanisms and pathways that support million-fold concentration gradients of dissolved marine solutes.

Karasov's chapter on nutrient transport among vertebrate intestines complements many medically oriented reviews already available; the present chapter focuses on the comparative and environmental aspects of transport. Specifically, Karasov provides a survey of digestive tract morphologies (where sugar and amino acid absorptions occur) among vertebrate groups, discusses some transport pathways and regulation mechanisms for sugar and amino acid absorption among species, and describes adaptations of intestinal nutrient transport in response to environmental factors. Although specific cellular uptake mechanisms are not emphasized, this chapter strongly addresses the more global issue of the importance of the intestine as a key organ in an animal's adaptation strategy in a given environment.

The chapter on mammalian hibernation is an obtuse inclusion in a book that centers on transport. Nonetheless, this chapter provides a wonderful overall integration of all physiological concepts and should be read by all who claim to be mammalian physiologists, whether zoological or medical. Within the paradigm of the hibernation cycle, Wang covers organ system physiology (cardiovascular, respiration, nervous system, and so on), neuroendocrine signals and feedback, thermoregulation, and cellular physiology (metabolism and enzymes, membrane mechanisms of fluidity modulation, ion pumps).

Water vapor absorption is rigorously reviewed in a chapter by O'Donnell and Machin. These authors describe the significance, mechanisms, and plumbing strategies of vapor absorption employed by terrestrial invertebrates. Arguments are presented for and against solute-dependent water vapor absorption, but detailed descriptions are not delineated regarding the epithelial and cellular putative mechanisms of water transport in invertebrated; an emphasis in this area may have rounded out the transport theme started by other chapters.

The final chapter by Bouquegneau and Joiris concerns the fate of heavy metals and organochlorines in marine organisms. With a little imagination, this topic may be loosely tied to the transport theme, because of the transfer of pollutants via alimentation and direct uptake from the environment. Membrane or tissue uptake mechanisms are not discussed per se; instead, the chapter emphasizes the dynamics and distribution of pollutants as a function of species, organs, age, seasonal variation, and environmental loads. The authors describe the concept of biomagnification of pollutants and discuss the significance of accumulation and distribution kinetics within an ecosystem.

In summary, this book is an excellent, though diverse, collection of reviews covering important and rigorously investigated disciplines of comparative and environmental physiology.

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BOOKS RECEIVED

Neuromethods. Volume 12. Drugs as Tools in Neurotransmitter Research. A. A. Boulton, G. Baker, and A. V. Juorio (editors). Clifton, NJ: Humana, 1989, 528 pp., illus., index, $84.50.

Methods in Enzymology. Volume 169. Platelets: Receptors, Adhesion, Secretion, Part A. Jacek Hawiger (editor). San Diego, CA: Academic, 1989, 512 pp., illus., index, $65.00.

Ecophysiology of Desert Vertebrates. P. K. Ghosh and Ishwar Prakash (editors). Jodhpur, India: Scientific, 1989, 475 pp., illus.

Sleep. J. Allan Hobson. New York: Freeman, 1989, 213 pp., illus., index, $32.95.

Toxicologic and Pharmacologic Principles in Pediatrics. Sam Kacew and Simon Lock (editors). New York: Hemisphere, 1988, 314 pp., illus., index, $59.50.

Sparse Distributed Memory. Pentti Kanerva. Cambridge, MA: MIT Press, 1989, 155 pp., illus., index, $24.95.

High Altitude Medicine and Physiology. Michael P. Ward, James S. Milledge, and John B. West. Philadelphia, PA: University of Pennsylvania Press, 1989, 515 pp., illus., index, $89.95.

Clinical Respiratory Physiology. Aubrey E. Taylor, Kai Rehder, Robert E. Hyatt, and James C. Parker. Philadelphia, PA: Saunders, 1989, 300 pp., illus., index, $19.95.

Genes and Signal Transduction in Multistage Carcinogenesis. Nancy H. Colburn (editor). New York: Dekker, 1989, 480 pp., illus., index, $125.00.

Natural Computation. Whitman Richards (editor). Cambridge, MA: MIT Press, 1989, 561 pp., illus., index, $25.00.

Neural Connections, Mental Computation. Lynn Nadel, Lynn A. Cooper, Peter Culicover, and R. Michael Harnish (editors). Cambridge, MA: MIT Press, 1989, 355 pp., illus., index, $39.95.

Nucleic Acid and Monoclonal Antibody Probes. Bala Swaminathan and Gyan Prakash (editors). New York: Dekker, 1989, 752 pp., illus., index, $150.00.

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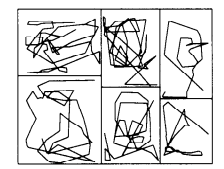

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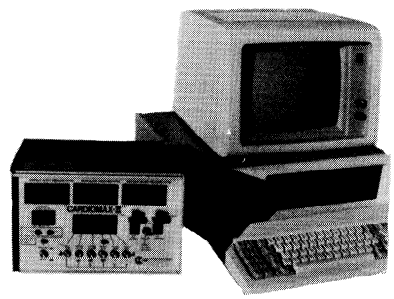

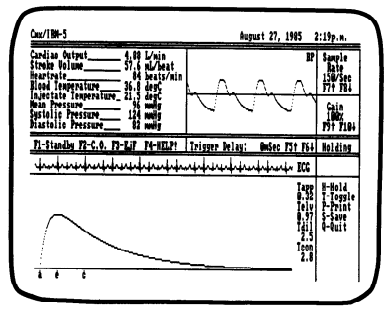

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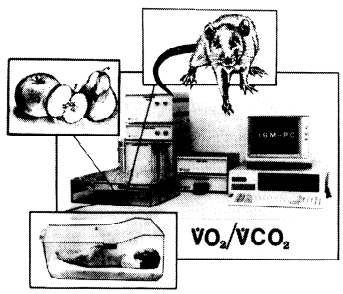

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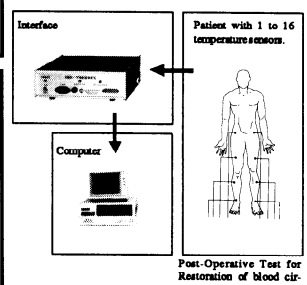

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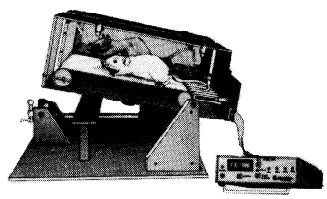

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The Search Committee of the Federation of American Societies for Experimental Biology (FASEB), with headquarters in Bethesda, Maryland, invites nominations and applications for the position of Executive Director, with duties to commence January 1, 1990.

As Chief Operating Officer of the Federation, the Executive Director is responsible for implementing the policies established by the FASEB Board and its Executive Committee. The Executive Director is expected to promote the purposes of the six Constituent Societies and one Affiliate Society, which comprise FASEB. The activities of FASEB include:

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- Promoting the aims and goals of the working scientists who make up FASEB.
- Contributing toward the attainment of the individual objectives of the Constituent Societies.
- Communicating scientific information through meetings and publications.
- Serving government, academic and industrial sectors, and the public.

The Executive Director is responsible to the Board for the management of FASEB headquarters (about 130 employees and a budget in excess of $12 million per year). He/she will participate with the Executive Officers of the Constituent Societies toward the attainment of their objectives. The Executive Director will keep informed of developments in government relevant to the pursuit of biological science, in general, and to FASEB and its members, in particular, and will make recommendations concerning their impact to the Executive Committee and Board. With their concordance, he/she will represent the Board and will transmit policy to external agencies.

With a membership of more than 30,000 biological scientists, FASEB occupies a crucial position in the scientific community in representing the views of research workers to government officials responsible for establishing scientific policies and the funding of research. As it enters the last quarter of its first century, FASEB, through its Executive Director, is heavily engaged in advocating positions of biological scientists on the proper use of animals in research and on the safe use of radioactive and potentially harmful chemicals. In particular, FASEB is very active in considerations of policies and regulations aimed at deterring misconduct in science, so as to ensure that new rules do not impede scientific inquiry. Participation in this process is viewed as challenging and essential for maintaining an atmosphere conducive to creative, innovative science.

In addition to a background in the biomedical sciences, knowledge of science policy and senior-level management experience, applicants should possess the attributes of vision, leadership, and motivation and have demonstrated the administrative and diplomatic skills to work harmoniously with groups having diverse interests and needs.

Salary and perquisites, in the range of those for top-level academic and research administrators, will be commensurate with the duties and responsibilities of the position and the qualifications and experience of the individual selected. Applications and nominations, submitted by August 15, 1989, should include a résumé of professional experience, a current curriculum vitae, a statement outlining reasons the position is of interest, and the names and addresses of three references.

This material should be directed to the attention of Dr. Howard K. Schachman, Chairman of Search Committee, Personnel Office, FASEB, 9650 Rockville Pike, Bethesda, MD 20814. [EOE]

Cardiologist, Internal Medicine. The University of California, Davis, School of Medicine is recruiting for a full-time academic position in the Division of Cardiology, Department of Internal Medicine. The position will be Open Rank in the Clinical or In-Residence series. Applicants should be board certified in Internal Medicine and either board eligible or board certified in Cardiovascular Medicine. Expertise in cardiac catheterization and angioplasty is required. The individual recruited will assist in organizing and developing an angioplasty service in conjunction with other cardiologists in the Division of Cardiovascular Medicine. Other divisional duties will include teaching, research, and development of a private practice clinic. Letters of interest, including a complete curriculum vitae, should be forwarded to Zak Vera, MD, Chair, Cardiology Search Committee, Room 2040, Professional Building, 4301 X Street, Sacramento, CA 95817. Position open until filled—applications will not be accepted after December 1, 1990. [EOAAE]

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Positions Available

There is a $25 charge per issue for each position listed. A check or money order payable to the American Physiological Society must accompany the copy. Purchase orders will not be accepted unless accompanied by payment. Ads not prepaid will not be printed. Copy must be typed double-spaced and limited to 150 words. All copy is subject to the editorial policy of *The Physiologist*. EOAAE indicates Equal Opportunity/Affirmative Action Employer and appears only where given on original copy. Copy deadline: copy must reach the APS office before the 15th of the month, 2 months preceding the month of issue (e.g., before February 15 for the April issue). Mail copy to APS, 9650 Rockville Pike, Bethesda, MD 20814.

Future Meetings

1989	
APS Fall Meeting	October 15–18, Rochester, MN
1990	
FASEB Annual Meeting	April 1–5, Washington, DC
APS Fall Meeting	October 6–10, Orlando, FL
1991	
FASEB Annual Meeting	April 21–26, Atlanta, GA
APS Fall Meeting	September 29–October 3, San Antonio, TX
1992	
FASEB Annual Meeting	April 5–9, Anaheim, CA
1993	
FASEB Annual Meeting	March 28–April 1, New Orleans, LA

ANNOUNCEMENTS

FASEB/LSRO

Reports Available

LSRO has completed a report for the FDA entitled **"Estimation of Exposure to Substances in the Food Supply."** It is based on the discussions of an ad hoc expert panel that explored issues and approaches involved in estimating human exposure to substance in the diet. The report is available at a cost of $20.00 prepaid for the FASEB Special Publications Office, 9650 Rockville Pike, Bethesda, MD 20814. (Maryland residents please add 5% sales tax.)

LSRO announces the availability of the proceedings of **"The Role of Folate and Vitamin B12 in Neurotransmitter Metabolism and Degenerative Neurological Changes Associated with Aging,"** a two-day workshop sponsored by the National Institute on Aging and the National Institute of Diabetes and Digestive and Kidney Diseases. Copies of the report are available for $25.00 prepaid from the FASEB Special Publications Office.

LSRO announces the availability of a report entitled **"Total Water and Tapwater Intake in the United States: Population-Based Estimates of Quantities and Sources."** The report is based on analysis of data collected during the 1977–78 Nationwide Food Consumption Survey (NFCS) of the US Department of Agriculture. Copies of the report are available from the FASEB Special Publications Office at a cost of $30.00 prepaid. (Maryland residents add 5% sales tax.)

New Studies

The Life Sciences Research Office, FASEB, is initiating two new studies for the Center for Food Safety and Applied Nutrition, FDA. The first, **"Outside Scientific Expertise on Nutrition Objectives for the Year 2000,"** requires review and evaluation by an ad hoc expert panel of a set of future national nutrition objectives that is being formulated by an interagency government working group as part of the US Public Health Service program to establish National Health Objectives for the Year 2000.

The second study, **"Emerging Food Safety and Quality Issues for the Next Decade,"** will identify and categorize the issues and resources that the scientific community considers of primary importance to the FDA in addressing its future responsibilities for research and education on, and regulation of, food safety and quality. *Information:* Kenneth D. Fisher or John M. Talbot, LSRO, FASEB. Phone: (301) 530-7030.

Scientific Meetings and Congresses

New York Academy of Sciences Conference on The Biological Actions of Extracellular ATP. Philadelphia, Pennsylvania, November 27–29, 1989. *Information:* Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021. Phone: (212) 828-0230.

New York Academy of Sciences Conference on Presynaptic Receptors – An Examination of Different Views. New York, December 6–8, 1989. *Information:* Public Relations Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021. Phone: (212) 838-0230.

1989 Centennial Meeting of the American Society of Zoologists and American Microscopical Society, American Behavior Society, The Crustacean Society, International Association of Astacology, and Society of Systemic Zoology. Boston, Massachusetts, December 27–30, 1989. *Information:* Mary Adams-Wiley, Executive Officer, American Society of Zoologists, 104 Sirius Circle, Thousand Oaks, CA 91360. Phone: (805) 492-3585. FAX: (805) 492-0370.

Third International Symposium of the Physical Medicine Research Foundation on Nerves, Muscles, and Joints; Chicken or the Egg? Vancouver, British Columbia, June 1–3, 1990. *Information:* Marc White, Executive Director, Physical Medicine Research Foundation, Suite 510, 207 West Hastings Street, Vancouver, British Columbia, Canada V6B 1H7. Phone: (604) 684-4148. FAX: (604) 684-6247.

Ninth International Congress of Eye Research. Helsinki, Finland, July 29–August 4, 1990. *Information:* 9th ICER Secretariat, Eye Research Laboratory, University of Helsinki, Siltavuorenpenger 20 A, SF-00170, Helsinki, Finland. Phone: 358-0-652570. FAX: 358-0-174072.

DRG Publication Available

A new edition of the statistical chartbook **DRG Peer Review Trends** is now available. This edition focuses on the characteristics of members of DRG study sections and Institute review groups and has a new section about members of NIH Advisory Councils and Boards from 1977 to 1986 (FY 87). Copies can be obtained from Information Systems Branch, DRG, Room 1A15, Westwood Building, Bethesda, MD 20892. Phone: (301) 496-7561.

Know Your Sustaining Associates

American Medical Association

The American Medical Association promotes the art and science of medicine and the betterment of public health. The AMA accomplishes this mission by advancing standards of medical education, promoting support for biomedical research, representing the medical profession, providing information about medical matters, and upholding professional conduct and performance.

Beckman Instruments, Inc.

Beckman Instruments, Inc. is a major international manufacturer of bioanalytical and diagnostic instruments and related products for science and medicine. The company was founded in 1935 by Dr. Arnold Beckman, who was inducted into the National Inventors Hall of Fame on Feb. 8, 1987. In 1982, the Orange County-based company merged with Smith Kline in Philadelphia to form SmithKline Beckman Corporation, a leading health care and life sciences company recognized worldwide.

Beckman's business is to combine chemistry and engineering. Its product lines include hundreds of instruments and related products. For the life sciences, Beckman manufactures centrifuges, liquid scintillation counters, spectrophotometers, and pH meters. For health care, the company produces clinical systems, diagnostic kits, reagents, and quality controls. A complete sales and service force supports Beckman customers.

Berlex Laboratories

Berlex Laboratories is a US subsidiary of the multinational pharmaceutical and chemical firm Schering AG West Germany (not connected with Schering-Plough Corp. or Schering Corp. of New Jersey). It conducts research and markets prescription drug products primarily for cardiovascular, diagnostic imaging, metabolic, endocrine, and central nervous system uses.

Coulbourn Instruments, Inc.

Coulbourn Instruments, Inc. manufactures electronic instruments for in vivo life science applications. Products include the LabLinc Modular Instrument System for physiological signal conditioning, experiment control, and data acquisition, featuring over 100 modules, including computer interface ports, signal conditioning and processing, and counting and timing modules for chart and computer-based polygraphs.

The company also produces transducers, biotelemetry, signal processors, stimulators, and auditory and animal behavior test equipment.

Major markets include pharmaceutical, chemical, and biotechnological firms, universities, research hospitals, and government laboratories.

Dagan Corporation

Dagan Corporation manufacturers electronic instruments used in electrophysiology. Dagan offers a full line of analog and digital products, including preamplifiers for use in intracellular and extracellular recording, single and two electrode voltage/current clamps, patch clamps/whole-cell clamps, signal averagers, programmable multichannel stimulators, and iontophoresis generators.

Glaxo, Inc.

Glaxo Inc., a leading research-based pharmaceutical company headquartered in Research Triangle Park, North Carolina, manufactures and markets prescription medicines including treatment for respiratory ailments, ulcers, hypertension, infectious diseases, and diseases of the skin. Glaxo is a wholly owned subsidiary of Glaxo Holdings p.l.c.

Grass Foundation

The Grass Foundation underwrites the annual Walter B. Cannon Lectureship given at the Spring Meeting of the American Physiological Society. The naming of this lectureship serves two functions: to commemorate the enormous contribution of Dr. Cannon to the growth of knowledge of physiology and to pay a tribute to Dr. Cannon on behalf of many of the founding trustees of the Grass Foundation who were members of his research group at Harvard Medical School early in their careers.

This lectureship is in accordance with the Grass Foundation's charter mandate to support research and education in neurophysiology. Other programs include funding for other annual and visiting lectureships, summer fellowship support for young students, and occasional relevant course support.

Harvard Apparatus

Harvard Apparatus, since its inception in 1904 at the Harvard Medical School, continues to design, develop, and supply the unique apparatus that has shaped the development of teaching and research in physiology and allied science, including syringe peristaltic and respiration pumps, recording systems, and research accessories.

ICI Pharmaceuticals Group

The ICI Pharmaceuticals Group R&D facility is based in Wilmington, Delaware. It consists of about 700 staff, of whom about 170 are in drug discovery. Within ICI, the US drug discovery function has sole responsibility for discovering new drugs in the pulmonary and CNS therapeutic areas. Current CNS targets are nondyskinetic antipsychotic drugs, disease-modifying drugs for Alzheimer's disease, and drugs for cerebral stroke and ischemia. The entire gamut of experimental approaches is available, including biochemical, neurochemical, electrophysiological, histochemical, and behavioral. Subserving the discovery efforts are a Molecular Pharmacology Unit at Wilmington and a Biotechnology Department in ICI-UK.

Jandel Scientific

Jandel Scientific designs and sells IBM-compatible software for scientific research. Products include Sigma-Plot for publication-quality scientific graphs (with automatic error bars, regression lines, and many other scientific graphing options); Sigma-Scan for *x-y* digitizing, morphometric measurement, and analysis; and PC3D for generating three-dimensional reconstructions of objects from serial sections. JAVA, the latest product, is a video analysis system capable of image processing, densitometry, automatic object counting and edge tracking, and morphometric measurement. JAVA works with a video digitizing board and input from a video camera, VCR, or other video source.

Janssen Pharmaceutica

Janssen Pharmaceutica was founded in Belgium in 1953 by Dr. Paul Janssen. It is now an international company built on the foundation of research and a bedrock of innovation. The company remains under the direction of Dr. Paul Janssen and has an unparalleled record in the successful development and marketing of new pharmaceutical products. According to the Japan Drug Research studies, Janssen was responsible for more significant new drug discoveries during the period 1970–1983 than any pharmaceutical company in the world.

The company currently has approximately 6,000 employees worldwide. It

is a world leader in medication used in the treatment of allergies, mental disorders, digestive and intestinal problems, cardiovascular conditions, and worm and fungal infections. Janssen's compounds have also enabled major advances in anesthesia and immunology. In addition, Janssen has also discovered many chemical compounds to identify and characterize receptors in the brain and the periphery that have played a prominent role in advancing our knowledge about neurotransmitters.

R. W. Johnson Pharmaceutical Research Institute

Ortho Pharmaceutical Corporation is now a part of the R. W. Johnson Pharmaceutical Research Institute. It is headquartered in Raritan, New Jersey and is a research-based pharmaceutical company engaged in the development and manufacture of a wide range of health care products marketed in more than 60 countries around the world. A wholly owned subsidiary of Johnson & Johnson, R. W. Johnson Pharmaceutical's operating divisions produce a variety of contraceptives, gynecological therapeutics, prescription and proprietary skin-care products, self-care diagnostics, and a growing number of biotechnology-derived pharmaceuticals, including immunomodulators and monoclonal antibodies.

With more than 4,000 trademarks registrations worldwide, R. W. Johnson Pharmaceutical continues its commitment to an intensive research and development program to ensure tomorrow's innovative health care products in the areas of conception control, immunobiology, and the treatment of gastrointestinal disorders and cardiovascular disease.

Narco Bio-Systems

Narco Bio-Systems designs, manufactures, and distributes the Physiograph® physiological recording systems for use in clinical, research, and teaching applications. A selection of multichannel chart recorders are available with a complete line of modular input preamplifiers, signal conditioners, transducers, and accessories. This allows maximum flexibility for designing systems for recording physiological functions.

Pennwalt Pharmaceuticals

Pennwalt Pharmaceuticals Division, based in Rochester, New York since 1886, has continually been committed to provide physicians and consumers with excellent products. In addition to providing fine pharmaceuticals, Pennwalt has become a leader in the technology of controlled drug delivery systems. Existing or imminent consumer and prescription products include agents to treat cardiovascular and neurological diseases, pain, infections, immunological disturbances, eating disorders, colds, and allergy. Current research promises to yield additional and products targeted for these therapeutic areas.

Pharmacia

Pharmacia is the world's leading supplier of separation and purification products for the biotechnology industry as well as a research-intensive international manufacturer of products for use in areas of medicine, including gastroenterology, rheumatology, oncology, ophthalmology, blood volume replacement, allergy, and dermatology.

Procter & Gamble Company

Procter & Gamble is a multinational, technically based consumer products corporation with operations in 28 states and 36 foreign countries. It has four technical centers, and its world headquarters are in Cincinnati, Ohio. Technical centers are also located in Egham and Newcastle, England; Brussels, Belgium; Schwalbach, Germany; and Osaka, Japan.

The world-wide PhD population of Proctor & Gamble is ~850, divided equally between chemists and life scientists, and total employees number 75,000.

Sales in the paper, soap and detergent, health care, personal care, pharmaceutical, beverage, and food categories make Proctor & Gamble one of the largest US corporations. *Fortune* magazine has named Proctor & Gamble as one of the most admired corporations in the United States.

Schering-Plough

Born out of a 1971 consolidation of two companies—Plough, Inc. and the Schering Corporation—Schering-Plough is dedicated to the discovery, development, and marketing of novel therapeutic entities. The company focused its research in the fields of anti-inflammatory, antiallergic, cardiovascular, and anti-infective disorders. The company has also attained a leading position in immunology and recombinant DNA technology.

Smith Kline & French

A division of Smith Kline Beckman Corporation, Smith Kline & French Laboratories is a technology-intensive, worldwide health care company. Smith Kline & French is a leading supplier of pharmaceuticals to treat infectious, gastrointestinal, cardiovascular, and arthritic diseases and a leader in the research, development and marketing of innovative medicines.

Squibb Corporation

Squibb Corporation is a research-based pharmaceutical company and a leading worldwide developer, manufacturer, and marketer of pharmaceutical and allied health care products. The Fortune 200 company has 18,000 employees in 27 countries and had sales of $2.6 billion in 1988. Its research, production, and marketing activities are directed from worldwide headquarters in Princeton, NJ.

Squibb offers over 1,000 products born of its research, including cardiovascular agents, antibiotics, insulins, ostomy care products, vitamins, psychotropics, veterinary medicines, radiopharmaceuticals, and surgical instruments.

APS Sustaining Associate Members

The Society gratefully acknowledges the contributions received from Sustaining Associate Members in support of the Society's goals and objectives
Second Century Corporate Founders indicated by asterisk.

American Medical Asssociation
Beckman Instruments, Inc.
Berlex Laboratories
*Boehringer Ingelheim
Burroughs Wellcome Company
Ciba-Geigy Corporation
Coulbourn Instruments, Inc.
Dagan Corporation
E. I. du Pont de Nemours & Company
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Gould, Inc.
Grass Foundation
Harvard Apparatus
Hoechst-Roussel Pharmaceuticals, Inc.
*Hoffman-La Roche, Inc.
ICI Pharmaceuticals Group
Jandel Scientific
Janssen Pharmaceutica
R. W. Johnson Pharmaceutical Research Institute
Lederle Laboratories
Lilly Research Laboratories
McNeil Pharmaceutical
*Merck & Co., Inc.
Miles Institute for Preclinical Pharmacology
NARCO Bio-Systems
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Pfizer Inc.
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Pillsbury Corporation
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Quaker Oats Company
*Sandoz, Inc.
*Schering-Plough Corporation
G. D. Searle and Company
Smith Kline & French Laboratories
*Squibb Corporation
Sterling Drug, Inc.
Sutter Instruments Company
*The Upjohn Company
*Warner-Lambert/Parke Davis
Waverly Press
Wyeth-Ayerst Laboratories

The Squibb Institute for Medical Research celebrated its 50th anniversary in 1988. Its achievements include the first large-scale production of penicillin, the development of a cure for tuberculosis, and the invention of a new class of antibiotics—the monobactams. A more recent breakthrough was the development of a new class of heart drugs known as ACE inhibitors. Capoten®, Squibb's ACE inhibitor for the treatment of hypertension and congestive heart failure, is the fourth-largest selling drug in the world.

The Upjohn Company

The Upjohn Company, a multinational corporation headquartered in Kalamazoo, Michigan, has celebrated its centennial year as a maker of fine pharmaceuticals. It is one of the 15 largest research-based pharmaceutical manufacturers in the world. It has research, production, and warehousing facilities in more than 45 countries and its products are sold in more than 150 countries.

Upjohn has long been committed to the research, development, manufacture, and marketing of pharmaceuticals. Human health care is the heart of Upjohn's endeavors.

Waverly Press

Approaching its 100th anniversary, Waverly Press is a full-service publication printer specializing in journals and other periodicals.

Committed to servicing its customers through sharing knowledge, providing the best of modern technology, and establishing mutual respect, Waverly Press offers a full range of publishing services including design, editing, composition, printing, binding, mailing and distribution, warehousing, subscription fulfillment, and ad sales.

Waverly practices team concept management. Both client and staff are part of the team. Through this management concept, each publication receives close personal attention.

Striving for excellence in the graphic arts industry is a tradition at Waverly Press—one that continues. Waverly believes in quality products and service through quality people.

FBR Ads Available

The three ads created last year by David Wojdyla of the advertising agency Bozell, Jacobs, Kenyon, and Eckhardt for the Foundation for Biomedical Research (FBR) are now available for purchase.

One shows animal activists protesting behind a police barricade. Above the photograph is the headline "Thanks to Animal Research, They'll Be Able to Protest 20.8 Years Longer."

Another ad shows microscopic views of a cancer cell, diseased heart tissue, and AIDS-infected lymphocytes. Above these is the headline "If We Stop Animal Research, Who'll Stop the Real Killers?"

The other ad shows a little girl propped up on pillows, cuddling her stuffed animals. The headline reads "It's the Animals You Don't See That Really Helped Her Recover" (see facing page).

These ads are available as posters from FBR. The cost is $5.00 for a single copy, $15.00 for groups of 10 of the same ad. The address is Foundation for Biomedical Research, 818 Connecticut Avenue, NW, Suite 303, Washington, DC 20006. Phone: (202) 457-0654.

INSTRUCTIONS FOR APPLYING FOR APS MEMBERSHIP

One application form serves all membership categories. There are, however, specific sets of instructions for each category. Therefore, it is essential that sponsors and applicants carefully follow the specific instructions in their desired category.

GENERAL INSTRUCTIONS

Check the box indicating the category of membership for which you are applying. Type the requested information on the application. Fill out all applicable spaces. Only completed applications will be reviewed. **Do NOT include a curriculum vitae or reprints.**

Alien Residents. Alien residents of the United States must enter the Alien Registration Receipt Card number under the address block on the application. Canadian residents should furnish a copy of "Landed Immigrant Status" form. Mexican residents should furnish a copy of their form FM-2. Central and South American residents must provide documentation as required by their country/government.

The Bibliography must be submitted in the form found in the Society's journals. An example of the current form is:

JONES, A. B., and C. D. Smith. Effect of organic ions on the neuromuscular junction in the frog. Am. J. Physiol. 220:110-115, 1974.

DEADLINE DATES

Completed applications for Regular and Corresponding membership received between February 1 and July 1 are considered for nomination by the Council in the Fall. Regular and Corresponding membership applications received between July 1 and February 1 are considered for nomination by the Council at the Annual Spring Meeting. Associate, Associate Corresponding and Student applications are accepted monthly upon approval of the Executive Director of the Society. Applications are not complete until all materials, including sponsors' letters, are received.

QUALIFICATIONS (Except Students)

The following categories are used when evaluating an application:

1. **Educational History.** Academic degree and postdoctoral training are evaluated and assessed with regard to how closely the applicant's training has been tied to physiology.

2. **Occupational History.** Particular emphasis is given to those applicants who have a full-time position in a department of physiology, or closely allied field. Relatively high ratings are given to individuals with positions in clinical departments and to those functioning as independent investigators in commercial or government laboratories.

3. **Interest in the Society.** Evaluation of this category is based on attendance at APS meetings and the applicant's remarks in the statement of "Interest in the Society."

4. **Interest in and Commitment to Teaching Physiology.** This evaluation is based on: (1) the fraction of the applicant's time devoted to teaching, (2) publications related to activities as a teacher including production of educational materials, and (3) special awards or other recognition the applicant has received for outstanding teaching effectiveness.

5. **Contributions to Physiological Literature.** This category is of major importance. The applicant's bibliography is evaluated on the basis of publications in major, referred journals which are concerned with problems judged to be primarily physiological in nature. Emphasis is given to papers published as the result of original research. Publications on which the applicant is sole author or first author are accepted as clear evidence of the applicant's independence.

6. **Special Considerations.** This category permits the Membership Committee to acknowledge unique accomplishments of an applicant. Such accomplishments may be excellence in a specific area, unusual contributions to physiology resulting from talents, interest or background substantially different from the average.

In general, persons who qualify for **Regular membership** will have a doctoral degree in physiology or related area and will have published several papers in referred journals. It should be clear that they have played a major role in research. They should have a position other than as a trainee in physiological research, teaching, administration, or related area.

Individuals who qualify for **Corresponding membership** should meet the requirements for Regular membership and live outside of The Americas.

In general, applicants will be considered for **Associate membership** if they have an advanced degree in physiology or related area and are doing research and/or teaching of physiology. Professional historians are eligible for Associate membership. Associate members may later be proposed for Regular membership.

Individuals considered for **Associate Corresponding membership** should meet the requirements for Associate membership and live outside of The Americas.

Applicants will be considered for **Student membership** if they are actively engaged in physiologic work which should lead to an advanced degree in physiology or related area. No individual may remain in this category for more than five years, without reapplying.

SPONSORS

Each of the two sponsors are required to write a confidential letter concerning the candidate's qualifications, using the criteria described above. Only one letter is required for evaluating applicants for Student membership.

Primary responsibility for membership rests with the two sponsors who must be Regular members of the Society or, for applications for Corresponding member category, a Corresponding member and a Regular member. Emeritus and Honorary members also may serve as sponsors. Sponsors should discuss the appropriateness of the class of membership with prospective applicants.

Each sponsor must write a confidential letter concerning the candidate which addresses the six categories listed above. An original and seven copies should be sent to the Membership Secretary. In the case of student applicants, two sponsors must sign the application form however, only one sponsor letter is required.

CHECK LIST

1. Original copy of the application signed by both sponsors.
2. Application form, including bibliography (1 original and 7 copies.
3. Mail the original, signed by two sponsors, plus 7 copies to: Membership Secretary, American Physiological Society, 9650 Rockville Pike, Bethesda, Maryland 20814.

RIGHTS AND PRIVILEGES OF EACH MEMBERSHIP CATEGORY

REGULAR MEMBERSHIP

1. Hold elective office.
2. Vote at Society meetings.
3. Serve on committees, boards and task forces.
4. Serve on Federation boards and committees.
5. Serve as sponsor on membership applications.
6. May present only one contributed paper, but may co-author and/or sponsor more than one contributed paper by a non-member at the Annual Spring (FASEB) and Specialty Meetings of the Society.
7. Receive *The Physiologist, NIPS,* and *Advances in Physiology Education.*
8. Receive the *FASEB Journal,* the FASEB Public Affairs Newsletters, and the annual FASEB Membership Directory.
9. Subscribe to books and periodicals published by the Society at member rates.
10. Register to attend scientific meetings of FASEB and APS at membership rates.
11. Participate in FASEB Member's Life Insurance Program, Disability Program and Hospital Protection Plan. (For residents of the United States, it territories or possessions).
12. Eligible to receive the Daggs Award.
13. Eligible to be selected as Bowditch Lecturer (members under 40 years of age).

CORRESPONDING MEMBERSHIP

1. Serve on Society committees, boards, and task forces.
2. Serve as one sponsor for a Corresponding membership application (one Regular member must be the other sponsor of a Corresponding member).
3. May present only one contributed paper, but may co-author and/or sponsor more than one contributed paper by a non-member at the Annual Spring (FASEB) and Specialty Meetings of the Society.
4. Receive *The Physiologist, NIPS* and *Advances in Physiology Education.*
5. Receive the *FASEB Journal* and annual FASEB Membership Directory.
6. Subscribe to books and periodicals published by the Society at member rates.
7. Register to attend scientific meetings of FASEB and APS at member rates.

ASSOCIATE MEMBERSHIP

Same as for Regular members with the following exclusions:

1. Holding elective office, or membership on certain committees.
2. Voting at Society meetings.
3. Sponsoring membership applications.
4. Eligibility for receiving the Daggs Award.
5. Privilege of selection as Bowditch Lecturer.
6. May sponsor only those abstracts on which they are listed as first author or co-author.

ASSOCIATE CORRESPONDING MEMBERSHIP

Same as for Associate members with the exception of receiving the FASEB Public Affairs Newsletter.

STUDENT MEMBERSHIP

1. Present one contributed paper at the FASEB and APS Meeting with the endorsement of the student's advisor.
2. Receive *The Physiologist, NIPS* and *Advances in Physiology Education.*
3. Subscribe to books and periodicals at member rates.
4. Register to attend scientific meetings of FASEB and APS at student rates.

THE AMERICAN PHYSIOLOGICAL SOCIETY

R-5/89

THE AMERICAN PHYSIOLOGICAL SOCIETY

9650 Rockville Pike, Bethesda, MD 20814

Date _____ LAST NAME _____

MEMBERSHIP APPLICATION

Submit original and 7 copies of application and supporting documents

REGULAR	☐	ASSOCIATE	☐
CORRESPONDING	☐	ASSOCIATE CORRESPONDING	☐
		STUDENT	☐

Current Membership and year elected _____

Refer to Instructions Before Continuing

Name of Applicant: _____

First Middle Last

Mailing _____ Birth Date: _____

Address _____ Citizenship: _____

_____ *Country of Permanent Residence:

_____ _____

*Alien Residents of The Americas enter proof of permanent residency or attach documentation. _____

1. EDUCATIONAL HISTORY

Dates	Degree	Institution	Major Field	Advisor

Doctoral Dissertation Title (if any): _____

_____

Postdoctoral Research Topic: _____

_____

SPONSORS

#1. Name: _____ #2. Name: _____

Mailing Address: _____ Mailing Address: _____

_____ _____

_____ _____

_____ _____

Telephone No. Telephone No.

I have read the guidelines and this application and attest that the applicant is qualified for membership.

#1 Signature _____ #2 Signature _____

Each sponsor must submit an original and 7 copies of a confidential letter of recommendation to the Society.

NAME _____

2. OCCUPATIONAL HISTORY

Present Position: _____

_____

Prior Positions:

Dates	Title	Institution	Department	Supervisor

3. INTEREST IN THE SOCIETY

a. Have you attended meetings of the APS (Y/N)? _____

b. In the space provided state why you want to join the Society.

4. TEACHING

a. Do you teach physiology (Y/N)? _____

b. What percentage of your time/effort is devoted to teaching (lectures, conferences, etc.) physiology? _____

c. Do you supervise graduate and/or postgraduate students (Y/N)? _____

d. Have you produced teaching aids (textbook chapters, films, computer assisted instruction, etc.) (Y/N)? _____

5. RESEARCH

a. What percentage of your time/effort is devoted to research? _____

b. If your research is funded state source: _____

Are you a principal _____ or co-principal investigator _____ ?

6. BIBLIOGRAPHY

On a **separate sheet** list your publications reported during the past 5 years. Star those in refereed journals.

R-5/89

Fall Meeting
American Physiological Society
and
American Thoracic Society

Mayo Civic Center
Rochester, Minnesota
October 15–18, 1989

For information on Fall Meeting registration, call the APS Fall Meeting Office (301) 530-7010.
For information on the meeting program, call the Membership Services Department (301) 530-7171.

Special Events

Mayo Laboratory Tours

Monday, October 16, 4:00 PM–6:00 PM

Bowditch Lecture

Wednesday, October 18, 4:45 PM–5:30 PM
Mayo Civic Center, Theatre

APS Business Meeting

Wednesday, October 18, 5:45 PM–6:45 PM
Mayo Civic Center, Theatre

Lecture

Franklyn G. Knox
"History of the Mayo Clinic"
Wednesday, October 18
11:45 AM–12:15 PM

Society Program

Opening Reception

Sunday, October 15, 7:00 PM–11:00 PM
Kahler Hotel, Heritage Ballroom

APS Past President's Address and Societal Banquet

Tuesday, October 17, 7:00 PM–10:00 PM
Kahler Hotel, Heritage Ballroom

Invited Sessions

Monday AM

Plenary Session
Physiology of Smooth Muscle

Monday PM

Plenary Session
Imaging for Physiology

Tuesday AM

Symposia
Single Ionic Channels
Fundamentals of Imaging Biological Structures and Functions
Endothelium-Dependent Vasomotor Responses
Crossbridges in Smooth Muscle

Tutorial
A New Radio-Telemetry System for Chronic Measurement of Blood Pressure from Laboratory Animals

Debate
Cell-to-Cell Conduction Across Gap Junctions Can Account for Electrical Syncytial Properties of Gastrointestinal Muscle

Tuesday PM

Symposia
Magnetic Resonance Spectroscopy in Humans
Dynamics of Mucus Secretion
Signal Transduction in Smooth Muscle
Pulmonary Microcirculation: New Developments

Tutorial
Automated Data Acquisition and Analysis for the Non-Computer User

Wednesday AM

Symposia
Transmitter and Receptor Operated Channels in Smooth Muscle
Cellular Mechanisms Involved in the Production of Myogenic Vascular Tone
Contractile System Function and Regulation of Smooth Muscle
Organ Structure and Function by X-Ray CT and PET

Tutorial
Simultaneous Measurement and Automated Acquisition of Blood Flow Velocity, Organ Dimension, and Tissue Displacement

Wednesday PM

Symposia
Measurement of Myocardial and Lung Metabolism and Blood Flow With Positron Emission Tomography
Ionic Basis for Electrical Rhythmicity in Smooth Muscles
Signal Transduction and Calcium in Smooth Muscle
Regulation of Pulmonary Blood Flow in Asthma

Thursday AM

Symposia
New Techniques in Microscopy
Hormonal Regulation of Vascular Smooth Muscle Function
Regulation of Airway Smooth Muscle Responses I
Cellular Dynamics of the Pulmonary Artery I: Cell Biology

Thursday PM

Symposia
Regulation of Airway Smooth Muscle Responses II
Pulmonary Circulation
Imaging Physiological Processes in Cells
Cellular Dynamics of the Pulmonary Artery II: Signal Transduction

APS/ATS Fall Meeting
Mayo Laboratory Tours

Many research laboratories in the Departments of Physiology, Biophysics, Pharmacology, Biochemistry, Molecular Biology, Medicine, and Radiology of the Mayo Medical School will be open for tours and demonstrations during the 1989 APS/ATS Meeting. How-to sessions and work stations for computer-based image analysis of physiological function at the organ, cell, and subcellular levels will be conducted in several laboratories. Industrial exhibits of the latest instruments available in biomedical imaging studies will also be on display.

The tours are scheduled for 4–6 PM on Monday, October 16, 1989. The name of the researcher (followed by building name and floor number) is given, along with a description of the tour.

John Burnett (Guggenheim, 9)—**Neurohumoral mechanisms in integrative cardiorenal function.** Experiments will be conducted emphasizing ongoing imaging techniques for on-line visualization of cardiac function, measurement of renal function, both hemodynamic and excretory, with on-line dynamic recordings of renal interstitial pressure. Further, we will display various biochemical techniques employed for state-of-the-art evaluation of circulating hormonal factors that actively participate in this integrative function.

Tom Dousa (Guggenheim, 9)—**Studies conducted on specific segments of tubules microdissected from the collagenase-treated kidney** provide the most definitive localization and biochemical processes within the highly heterogenous mammalian nephron. We will have on display the instrumentation for microdissection of subsegments of collecting ducts from mouse kidney and instruments used for microanalysis of components of cyclic AMP metabolism. The principles of the procedures will be displayed. Merits and limitation of this methodology will be concisely summarized. A one-page summary handout, including basic references, will be available for visitors.

Franklyn Knox (Guggenheim, 9)—**Renal physiology of sodium and phosphate metabolism, micropuncture, microcirculation, renal interstitial pressure measurements, and infusions into the renal interstitium.** Demonstration of methods for the study of the relationship between the fluid dynamics of the renal interstitium and tubule transport. The materials and methods for matrix implantation in the renal interstitium and micropuncture of the renal tubules will be displayed.

Joe Szurszewski and Anthony J. Bauer (Guggenheim, 8)—**Whole cell and single-channel recording techniques** will be demonstrated on smooth muscle cells dissociated from the canine gastric antrum. The advantage of using nystatin to permeabilize on-cell membrane patches without loss of cytosolic enzymes and second messengers critical to ion channel function will also be demonstrated.

Joe Szurszewski and Henry Parkman (Guggenheim, 8)—**The nature and physiological function of peripheral reflex activity between abdominal sympathetic ganglia and the gastrointestinal tract** will be demonstrated with two types of experiments: *1*) physiological function of mechanosensory input from the colon and *2*) the effect of pressure application of putative peptidergic and nonpeptidergic transmitters on the excitability of sympathetic neurons and on ongoing mechanosensory synaptic input.

John Blinks (Guggenheim, 7)—**Calcium release by inositol 1,4,5-trisphosphate (IP_3) in amphibian and mammalian skeletal muscle** appears to be an artifact of cell disruption and probably results from IP_3-induced depolarization of sealed-off T-tubules. These conclusions have been drawn from experiments on intact single muscle fibers in which IP_3 has been microinjected under conditions chosen to test the involvement of the T-tubules. Videotapes of the experiments will be shown.

Stephen Brimijoin (Guggenheim, 7)—**Sympathetic dysfunction caused by autoimmunity to acetylcholinesterase.** Our demonstration will deal with the physiological effects of monoclonal antibodies to acetylcholinesterase injected iv into rats. The antibody recipients rapidly develop symptoms of sympathetic dysfunction, including ptosis and hypotension. Antibody-injected animals will be available for direct observation. Recordings of blood pressure and heart rate will be on display, along with the results of pharmacological experiments to identify the site of the immunological lesion.

David Clapham (Guggenheim, 7)—**Confocal microscopy enhances resolution by rejecting light scattered from out-of-focus regions of a specimen.** Imaging of cells and tissues is improved in both the *x-y* and *z* planes. By taking a series of confocal images and reconstructing a thick specimen from the individual segments, new information is obtained. A small artery will be studied with confocal microscopy and the specimen reconstructed in three dimensions. In this way the intracellular calcium concentration of the endothelium lining the artery can be contrasted to the underlying smooth muscle.

Stuart Taylor (Guggenheim, 7)—**Computer visualization and display of rapid events in living cells.** Mechanisms of excitation-contraction (EC) coupling in vertebrate muscle will be analyzed through computer-assisted measurements. Skeletal muscle cells, cardiac myocytes, and skeletal myoballs are

used to compare EC coupling in adult and primitive muscle. A unique computer system records and analyzes two-dimensional images in each contraction.

Frank Prendergast (Guggenheim, 5)—**Molecular motion in proteins:** experiments, calculations, and graphic displays. We will demonstrate how molecular dynamics calculations coupled with umbrella sampling techniques are being used to simulate intramolecular motion in protein. Time-resolved fluorescence anisotropy and NMR relaxation measurements provide the experimental counterpart to the simulations. The data are displayed by use of molecular graphics on raster and calligraphic sytems.

Garth Powis (Guggenheim, 4)—**Measurement of intracellular free Ca^{3+} in populations of normal and tumor cells** in response to growth factors using the photoprotein aequorin.

Barry Gilbert (Medical Sciences, 3)—**Special-purpose computer design, test, and assemble capabilities.** Our research group develops special-purpose digital computers for medical and nonmedical applications. We *1*) design the signal processors, *2*) simulate their behavior on general purpose VAX computers to assure that they will work as intended, *3*) design the individual integrated circuits, *4*) have the "chips" manufactured for us, *5*) package and test the fabricated chips in our Rochester laboratories, *6*) assemble the demonstration signal processor and test it. We use Gallium Arsenide (GaAs) instead of silicon "chips," because the GaAs devices perform at much higher throughput rates than silicon. The tour will demonstrate the methods by which we design, assemble, and test the "chips" and processors developed here.

Gertrude Tyce (Medical Sciences, 3)—**Metabolism of catecholamine and serotonin sulfates by the isolated perfused rat liver.** A high proportion (75%–95%) of plasma catecholamines are sulfoconjugated. It has often been suggested that sulfated catecholamines represent a reservoir from which free catecholamines can be generated by the action of sulfatase enzymes. A demonstration is given of the use of the isolated perfused rat liver system to study the metabolism of radiolabeled dopamine sulfate.

Jim Greenleaf (Medical Sciences, 1)—**Multidimensional imaging of the intact heart with ultrasound.** Stereo ultrasound images of the intact beating heart will be shown. Methods of obtaining the data will for described.

Erik L. Ritman (Medical Sciences, 1)—**In vivo pathophysiology visualized and analyzed using 3-D imaging and display.** The tour of this facility will include the "machine room" housing the 15-ton DSR scanner, the "interface room," which accesses the subject tunnel inside the scanner, the cardiac catheterization laboratory for preparing subjects about to be scanned, and the room housing the special purpose image reconstruction computer. Some representative image data generated with the scanner will also be on hand.

Richard Robb (Medical Sciences, 1)—**ANALYZE demonstration.** Featuring hands-on demonstrations of ANALYZE, a software package developed at Mayo for advanced biomedical imaging display, manipulation, and measurement. ANALYZE can be used to analyze 3-D imaging modalities based on X-ray computed tomography, radionuclide emission tomography, ultrasound tomography, magnetic resonance imaging, and both light and electron microscopy. The demonstration will illustrate the comprehensive, fully interactive capabilities of this system for exploration and quantitative investigation of biological structures and function.

Carlos Romero (Medical Sciences, 1)—**Three-dimensional canine renovascular structure and circulation visualized in situ with the dynamic spatial reconstructor.** Renovascular structure and circulation will be demonstrated using data obtained from the dynamic spatial reconstructor. Topics will include methods to visualize and to measure renal volume, opacity of renal tissue, and transit of contrast medium through the renal vasculature.

Julio M. Fernandez (Medical Sciences, 1)—*1.* **Patch-clamp measurements of exocytosis.** The cell membrane capacitance of single mast cells undergoing exocytosis will be measured with a combination of patch-clamp and circuit-analysis techniques. The fusion of individual secretory granules with the cell membrane is measured as a step increase in the cell's membrane capacitance. Granule attributes such as number, size, and rate of fusion will be demonstrated. *2.* **Optical sectioning of living secretory cells.** Beige mouse mast cells will be incubated with a fluorescent indicator dye that labels the secretory granules. Regularly spaced fluorescent images of the cells will be taken with a high-resolution, cooled CCD camera. A simple Fourier deblurring scheme will demonstrate a dramatic increase in image quality where the outlines of granules can be observed with 0.2-μm resolution in the living cell.

Stephen J. Riederer (Radiology Research Building)—**The activities of the MR Laboratory of the Department of Diagnostic Radiology** are primarily in the area of research in magnetic resonance imaging (MRI). Specific projects are in high-speed MR image acquisition and reconstruction, MR angiographic imaging, and adaptive techniques for motion correction. During the open house the facilities of the lab will be available for tour, and recent research results will be displayed and explained.

James H. Chesebro (Plummer, 6)—**A new nonisotopic in vivo technique for quantitating arterial smooth muscle cell proliferation.** We have developed a new in vivo technique for quantitating smooth muscle cell (SMC) proliferation using bromodeoxyuridine (BrdU), a halogenated analogue of thymidine, and immunohistochemical staining.

Paul Scanlon (Plummer, South, 3)—**The Mayo Pulmonary Laboratories** use both customized and commercially available equipment supported by locally developed computer

software to handle a large volume of routine studies as well as a large variety of special studies. The Routine Pulmonary Function Lab has recently installed new equipment with custom software developed jointly with the manufacturer. The Outreach Lab provides spirometry testing to a large number of medical and industrial subscribers. Other labs including Exercise, Blood Gas, Resting Energy Expenditure and Special Lung Mechanics will also be open to visitors.

M. Camilleri (Charlton, 2)—**Development of a method to noninvasive study transit in the unprepared human colon.** These studies demonstrate the in vitro dissolution characteristics of a medication gelatin capsule containing radiolabeled pellets and coated with pH-sensitive polymer, methacrylate. Preliminary in vivo studies in humans have validated the noninvasive, scintigraphic technique and have characterized and quantitated regional transit of solids in the unprepared colon of healthy human volunteers. These tracers are now used to study the effects of various physiological and pharmacological interventions of colonic transit and the effects of colonic diseases.

R. Gibbons (Charlton, 2)—**Quantitation of myocardial infarct size with Tc-99m labeled myocardial perfusion agents.** Demonstration of a simple technique for the estimation of percent infarcted myocardium from tomographic images of the heart obtained with Tc-99m labeled myocardial perfusion agents. The technique will be used to demonstrate the efficacy of acute thrombolytic therapy in patients with acute myocardial infarction.

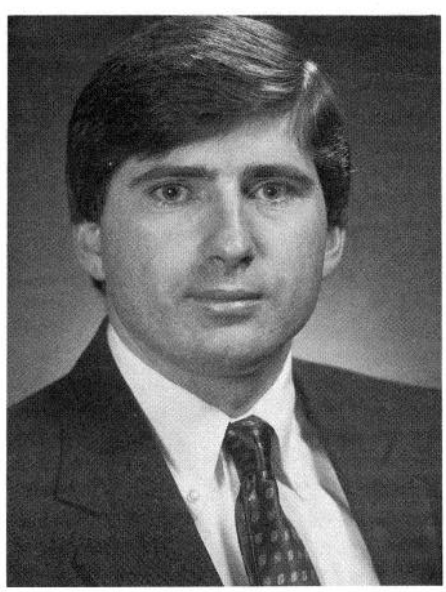
Michael O'Connor (Charlton, 2)—**Noninvasive quantitation of liver hemodynamics using radionuclide angiography.** Demonstration of the use of deconvolution analysis to permit the estimation of hepatic extraction efficiency for a Tc-99m labeled bilirubin analog and to measure total liver blood flow and hepatic arterial to portal venous blood flow ratio in humans.

H. Wahner (Charlton, 2)—**Transmission bone mineral analysis in osteoporosis.** Demonstration of the use of dual energy radiography and dual photon absorptiometry for bone mineral analysis of the lumbar spine and hips. The techniques are used to study the effects of various disease processes and therapies and the impact on bone loss.

John W. Shepard, Jr. (Colonial, 4)—We will provide an overview of the activities of the **Mayo Sleep Disorders Center,** as well as demonstrate our techniques of measuring pharyngeal pressures and cross-sectional areas of the upper airway with fiberoptic pharyngoscopy and fast CT scanning to evaluate regional compliance characteristics of the upper airway in normals and patients with obstructive sleep apnea.

John A. Rumberger (St. Marys Imaging Center, 6)—**The ultrafast-CT currently housed within the Imaging Center at Saint Marys Hospital** is a unique electron beam device that acquires multilevel tomographic images of the body at a rate of up to 17 frames per second allowing for characterization of cardiac and respiratory motion and flow. This device, while staffed by members of the Division of Diagnostic Radiology, is used for multidisciplinary studies by members of that division in close cooperation with members from the Divisions of Thoracic Diseases and Cardiovascular Diseases. Two major research topics include studies on the dynamics of obstructive sleep apnea and longitudinal studies of left ventricular remodeling following myocardial infarction. Additionally, customized image processing software is under development to facilitate these and other studies of cardiovascular physiology.

1989 Bowditch Lecture



Joey P. Granger, Eastern Virginia Medical School, will present the Bowditch Lecture entitled "Atrial Peptides in Volume and Pressure Regulation" at the APS/ATS Fall Meeting, Rochester, MN, on Wednesday, October 18, 1989, at 4:45 PM in the Theatre in the Mayo Civic Center.

Poster Sessions With Associated Abstracts

Tuesday

Wednesday

Thursday

14.1

MECHANISMS OF Ca^{2+}-ACTIVATION OF AEQUORIN-LOADED CANINE TRACHEAL SMOOTH MUSCLE BY MUSCARINIC AGONISTS. M.H. Al-Hassani*, J. Service*, J.Q. Stropp* and S.J. Gunst. Mayo Clinic and Foundation, Rochester, MN 55905

We investigated mechanisms of Ca^{2+}-activation by the muscarinic agonists acetylcholine (ACh) and McN-A-343 (McN). Both agonists activate M_3 receptors in canine tracheal smooth muscle. At comparable levels of active stress, ACh elicits a large transient rise in $[Ca^{2+}]_i$ and rapid force development, whereas McN causes slower force development and a gradual rise in $[Ca^{2+}]_i$. Responses to both agonists were similarly depressed by verapamil and diltiazem. However, Ca^{2+}-depletion experiments suggested contractions by ACh are slightly more dependent on the release of intracellular Ca^{2+} Isotonic shortening velocities (V_i) were measured during contractions with each agonist and compared with changes in $[Ca^{2+}]_i$. In ACh-contracted muscles, there was an initial transient rise in V_i to a maximum of 0.111 ± 0.011 L_o/s at 1 min which declined to 0.048 ± 0.007 L_o/s by 10 min (n=13). With McN, V_i reached a maximum of 0.050 ± 0.005 L_o/s at 1 min and declined to 0.025 ± 0.0055 L_o/s at 10 min. Phorbol dibutyrate (PDB) depressed the transient rise in $[Ca^{2+}]_i$ in ACh-contracted muscles and decreased the rate of force development. Results suggest that changes in V_i and $[Ca^{2+}]_i$ are correlated. PDB may depress the Ca^{2+} transient and the rate of contraction in response to ACh by suppressing IP_3-mediated release of intracellular Ca^{2+}. Supported by HL29289.

14.2

REGULATION OF THE CONTRACTILE SYSTEM IN COLONIC SMOOTH MUSCLE. W.T. Gerthoffer*, K.A. Murphey*, J. Mangini*, and F. Lattanzio*. (Spon. K. Sanders) Departments of Pharmacology, University of Nevada School of Medicine, Reno, NV 89557, and Eastern Virginia Med. School, Norfolk, VA 23323.

We investigated the time-dependence of lightly loaded Shortening velocity, myosin phosphorylation and myoplasmic Ca^{2+} ($[Ca^{2+}]_i$]) during contraction of circular muscle from canine colon. Shortening velocity was measured by quick-release to a 10% afterload. Myosin phosphorylation was measured by an immunoblot method, and changes in $[Ca^{2+}]_i$ were estimated by measuring fluorescence at 550 nm in strips loaded with fluo-3 (5 uM fluo-3/AM, 2-3 hr.). During tonic contractions induced by 60 mM K^+, phosphorylation increased from 0.097 ± 0.017 moles Pi/mole light chain to 0.295 ± 0.021 at 30 sec, and remained elevated. In contrast, velocity increased rapidly within 10 sec to 0.043 ± 0.004 lengths/sec and decreased exponentially to 0.017 ± 0.001 at 10 min. During transient contractions induced by 10 uM acetylcholine, phosphorylation increased slightly from 0.23 ± 0.03 to 0.35 ± 0.03 at 15 sec. In contrast, shortening velocity increased to 0.06 ± 0.015 lengths/sec within 2.4 sec, and decreased exponentially thereafter. Fluo-3 fluorescence increased in parallel with force during both tonic and transient contractions. During colonic muscle contraction, a transient increase in shortening velocity was observed without concurrent phosphorylation or $[Ca^{2+}]_i$ transients. (Supported by NIH grants HL35805 and DK41315).

14.3

INTRACELLULAR SODIUM AND ITS REGULATION IN SMOOTH MUSCLE CELLS. Edwin D.W. Moore* and Fredric S. Fay. Univ. Mass. Medical Center, Worcester, MA. 01655

We have measured $[Na^+]_i$ and studied $[Na^+]_i$ regulation in single, enzymatically dissected cells isolated from the stomach of the toad Bufo marinus. $[Na^+]_i$ was measured with the Na^+-sensitive fluorescent dye SBFI (sodium-binding benzofuran isophthalate). Cells were incubated at room temperature with the acetoxymethylester form of the dye; $[SBFI]_i$ < 900 µM. Cell images were captured on a digital imaging microscope using a cooled CCD camera. A high speed dual wavelength microfluorimeter was used for rapid (100ms) measurements of $[Na^+]_i$ from whole cells. The in vitro and the in vivo calibration curves of the dye are significantly different from one another, so we have developed a procedure for calibrating the dye from each cell as the terminal step in every experiment. Dye distributed throughout the cell but concentrated in the nucleus. Ratio images however indicate that $[Na^+]_i$ was uniform, 12 ± 4 mM (N=34). Blockade of the Na^+/K^+ ATPase by ouabain (100 µM) increased $[Na^+]_i$. Isoproterenol (100µM) however decreased $[Na^+]_i$; this effect was reversible and was completely blocked by 10 nM pindolol. This observation supports the hypothesis that ß-adrenergic relaxing agents stimulate the Na^+/K^+ ATPase, increasing the transmembrane Na^+ gradient which is used to extrude Ca^{2+} via Na^+/Ca^{2+} exchange. This work was supported by an MDA Fellowship (EDWM) and NIH-HL14523.

14.4

IMAGING DUAL WAVELENGTH FLUORESCENT PROBES IN LIVING CELLS AT VIDEO RATES.
Fernando Delaville*, Kevin E. Fogarty* and Fredric S. Fay. Dept. of Physiology, U.Mass. Medical Ctr., Worcester, MA 01655.

There is much interest in the use of dual wavelength fluorescent probes to determine the local concentration of ions and molecules; however, due to the low signal strength of fluorescence at the single cell level, current cameras and digital image processors yield useful information only at about 1 second resolution. Many biologically relevant changes take place much more rapidly, requiring a faster system. A Fast Digital Imaging Fluorescence Microscope capable of obtaining multi-spectral images at video rates has thus been developed. It records up to six minutes of data, switching excitation wavelengths between frames. This system incorporates commercially available equipment with custom circuitry and software to record freeze-frame images of 50 microseconds duration every thirtieth of a second. The components involved and the sources of noise have been characterized and their models used in off-line processing. The system will be demonstrated with calcium images obtained by loading single isolated smooth muscle cells with Fura-2. The signal to noise ratio of pixels in the final images has been calculated, and only statistically significant changes displayed. The system is capable of generating a "movie" where the images of calcium distribution can be seen changing with time.

14.5

ATP STIMULATES AN INITIAL TRANSIENT AND SUBSEQUENT OSCILLATIONS OF $[CA^{2+}]$ IN CULTURED ARTERIAL SMOOTH MUSCLE CELLS: A DIGITAL IMAGING STUDY. Catherine J. Randall*, Jennifer J. Linderman*, Linda L. Slakey* and David J. Gross* (SPON: D. N. Spinelli). Univ. of Massachusetts, Amherst, Ma. 01003.

We have examined the detailed kinetics of transients in intracellular calcium ion activity ($[Ca^{2+}]$) in individual adherent cultured aortic smooth muscle cells (ASMC) stimulated with ATP, which acts as a constrictor or relaxant and which is coreleased with some neurotransmitters. We measure $[Ca^{2+}]$ by imaging the fluorescence of fura-2 loaded ASMC, and computing $[Ca^{2+}]$ from the 334nm/365nm fluorescence ratio and calibration images (Linderman *et al.*, Cell Calcium, in press).

Upon addition of ATP (50nM-250µM) to the bathing medium, all ASMC produce a rapid rise in $[Ca^{2+}]$ to 500-1500 nM from resting levels of ~100 nM within ~2 sec followed by a decline over ~100 sec. Many, but not all, ASMC produce a subsequent train of $[Ca^{2+}]$ pulses of frequency ~1.3 min^{-1} which continue in the presence of ATP but are abolished in its absence. The initial $[Ca^{2+}]$ transient is synchronous in all ASMC, while the oscillations are asynchronous from cell to cell. Removal of extracellular Ca^{2+} can slow the oscillations and in some cases can abolish them.

Support: NIH HL-38130, NSF DMB-8803826.

14.6

INSTRUMENTATION FOR SIMULTANEOUS MEASUREMENT OF IONIC CURRENTS AND INTRACELLULAR FREE CALCIUM IN SMOOTH MUSCLE CELLS. M. Sturek and W.M. Caldwell (SPON: C.C. Hale). Dept. of Physiol. and Dalton Res. Ctr., Univ. of Missouri, Columbia, MO 65211.

Intracellular free Ca (Ca_f) was determined with fura-2 by use of sequentially switched sample-and-hold amplifiers to synchronize the measurement of fluorescence emission with the appropriate excitation wavelengths (340 and 380 nm). The circuits sample photomultiplier tube output and average the signals by a variable time constant, depending on rotation period of an interference filter wheel that is rotated by a motor with a highly precise speed controller. The separated fluorescence signals due to 340 and 380 nm excitation are then fed into an A-D converter and data acquisition and analysis is performed with commonly used pCLAMP software (Axon Instruments). The use of liquid light guides that transmit collimated light from a Xe arc source to the interference filters and the microscope enabled simple optical alignment and vibration isolation of the microscope during patch-clamp experiments. Ratio fluorescence measures can be obtained at 20 ms intervals. The system has enabled, for example, determination of the temporal relationship between Ca release from the sarcoplasmic reticulum and activation of non-selective cation channels in the sarcolemma of smooth muscle cells from the coronary artery. The system can be applied to other ion-sensitive fluorescent dyes for pH, Mg, and Na that also require dual wavelength excitation. Supported by Institutional Biomedical Research Support #RR 07053.

14.7

DISTRIBUTION OF Ca^{2+} IN CULTURED VASCULAR SMOOTH MUSCLE CELLS AT REST AND DURING ACTIVATION: COMPARISON OF TWO FURA-2 LOADING METHODS. William F. Goldman* and Mordecai P. Blaustein. Univ. of Maryland School of Medicine, Baltimore, MD 21201

The effect of two fura-2 loading methods on the apparent distribution of intracellular Ca^{2+} ($[Ca^{2+}]_{App}$) was studied in single cultured A_7r_5 cells using digital imaging microscopy. Fura-2 was introduced into cells either by incubation with its acetoxymethyl ester, fura-2/AM, or by transient ATP-induced permeablization of the sarcolemma such that the free fura-2 could enter the cell directly. $[Ca^{2+}]_{App}$ in unstimulated cells loaded by the former method was heterogeneous, reflecting, in part, separate pools of Ca^{2+} in the cytosol and the sarcoplasmic reticulum (SR). This was especially evident in the area of the nucleus where large differences existed between the nucleus, containing the lowest $[Ca^{2+}]_{App}$, and the SR-rich, perinuclear region containing some of the cells' highest $[Ca^{2+}]_{App}$. In contrast, $[Ca^{2+}]_{App}$ was uniform in cells loaded with fura-2 by transient permeablization; this reflected the restriction of fura-2 to the cytosolic compartment. $[Ca^{2+}]_{App}$ in these cells was substantially lower than mean $[Ca^{2+}]_{App}$ in fura-2/AM loaded cells, because SR Ca^{2+} influences the signal with fura-2/AM loading, but not with free fura-2 loading. The temporal and spatial distribution of $[Ca^{2+}]_{App}$ was similar for the two loading methods during serotonin-evoked Ca^{2+} transients, when the SR signal was dominated by the high cytosolic Ca^{2+}. However, after the Ca^{2+} transient, when $[Ca^{2+}]_{App}$ returned toward resting levels, the differences became apparent once more.

14.8

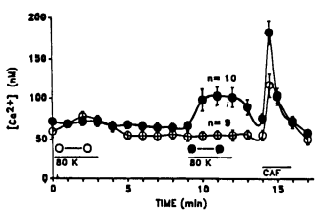
THE INHIBITORY EFFECT OF cAMP ON COLONIC SMOOTH MUSCLE IS NOT MEDIATED BY MODULATION OF CA^{2+} OR CA^{2+}-ACTIVATED K^+ CHANNELS. A. Kodner, E.A. Mayer, W.J. Snape, Jr., G. Sachs. Dept. of Medicine, Harbor-UCLA Medical Center, and Dept. of Physiology, UCLA, Los Angeles, Ca. 90024.

In intact tissue, activators of A kinase inhibit spontaneous and substance P-stimulated contractions of longitudinal colonic muscle. To determine if this inhibition is mediated by an increase in the open probability (P_o) of Ca^{2+}-activated K^+ channels, or by a decrease in dihydropyridine-sensitive Ca^{2+} influx, we studied whole cell and single channel currents in freshly dispersed myocytes from the rabbit longitudinal colon using the patch clamp technique. In cell-attached recordings, when bath and pipette contained a 126 mM KCl Ringer solution, and the patch was held at -70 mV, P_o of Ca^{2+}-activated K^+ channels was less than 0.01. Depolarization activated K^+ channels in a sigmoidal fashion, with a P_o of 0.38 at a membrane potential (V_m) of 50 mV. 8-bromo cyclic AMP (8-brcAMP) and dibutyryl cyclic AMP (dbcAMP) (both 10^{-3} M) when added to the bath had no effect on P_o at any V_m. In whole cell recordings, when the pipette contained a 140 mM CsCl solution with 2 mM ATP and 2.0 mM EGTA, depolarization activated dihydropyridine-sensitive Ca^{2+} current. Peak inward current was 58 ± 2 pA (mean ± S.E.;n= 6). 8-brcAMP or dbcAMP (both 10^{-3} M) when added to the bath did not affect Ca^{2+} currents V_m. In conclusion, these results suggest that the inhibitory effect of cAMP on colonic smooth muscle is not mediated by modulation of Ca^{2+} or Ca^{2+}-activated K^+ currents.

14.9

CALCIUM-FILLED SARCOPLASMIC RETICULUM IN CORONARY ARTERY SMOOTH MUSCLE CELLS MAY SLOWLY RELEASE CALCIUM TO THE EXTRACELLULAR SPACE. L. Stehno-Bittel*, M. Sturek (SPON: C.C. Hale). Univ. of Missouri, Columbia, MO 65211.

We tested the hypothesis that the Ca-filled sarcoplasmic reticulum (SR) of smooth muscle cells (SMC) releases Ca to the extracellular space at rest without elevating intracellular free Ca (Ca_i) in the bulk myoplasm. Ca_i was measured with fura-2 microphotometry in freshly dispersed porcine coronary artery SMC. At 14 min into both protocols shown in the Figure SMC were exposed to caffeine (CAF, 5 mM) for 2 min to release Ca from the SR. One group of SMC (open circles) was depolarized with 80 mM K to cause Ca influx and fill the SR with Ca, then allowed to recover 11 min; the other SMC (closed circles) were allowed to recover from depolarization only 2 min prior to CAF. SMC given the short, 2 min recovery responded with greater Ca_i increase to CAF than SMC given the long recovery. Furthermore, Ca_i levels remained constant during the 11 min recovery period prior to CAF, suggesting that Ca left the SR and did not accumulate in the bulk myoplasm. We interpret these results to be consistent with our hypothesis and suggest that the SR may serve a protective, Ca_i buffering role by extruding sequestered Ca from coronary SMC. Supported by AHA Missouri Affiliate.



14.10

FRESHLY DISPERSED CORONARY ARTERY SMOOTH MUSCLE CELLS DEMONSTRATE A CUMULATIVE RESPONSE TO REPEATED EXPOSURES TO ENDOTHELIN. C. Wagner-Mann*, L. Bowman*, and M. Sturek (SPON: C.C. Hale). Department of Physiology and Dalton Research Center, University of Missouri, Columbia, MO 65211

Ca regulation by serial exposures of freshly dispersed bovine and porcine vascular smooth muscle cells (SMC) to endothelin (EN, $1x10^{-8}$ M) were studied. Intracellular free Ca (Ca_i) was measured in single SMC using fura-2 fluorescence microphotometry. SMC underwent a series of exposures consisting of 80 mM K (80K, for 3 min), EN (for 4 min), 80K, and then EN; each exposure was preceded by a two min interval during which the SMC were bathed in a normal physiologic buffer to allow for re-establishment of baseline. Ca_i increases to the first and second 80K depolarizations were statistically equivalent (from resting value of 62.4±6.6 to 87.2±5.8 and 94.2±7.4 nM respectively; mean±SEM, n=13), demonstrating SMC viability. The SMC fell into two distinct groups with respect to the EN responses. One group of SMC demonstrated no measurable change in Ca_i with the first EN exposure, while the second exposure to EN elicited a significant increase in Ca_i over baseline (116.0±3.7%; n=6) with no return toward baseline once EN was removed from the bath. The second group of SMC responded with a statistically equivalent increase in Ca_i over baseline to the two EN exposures (150.6±17.7 and 147.7±7.6% respectively; n=7). In this second group, Ca_i returned to resting levels following the first EN exposure. Much like the first group, however, in the second group the increase in Ca_i associated with the second EN exposure was sustained even after EN was removed from the bath. It was concluded that EN's effects in the same SMC are cumulative when the SMC are challenged with serial exposures of EN. These findings suggest that different populations of SMC exist within the same segment of coronary artery and may help resolve discrepant studies showing transient and sustained responses to EN. Supported by AHA Missouri Affiliate.

14.11

DEVELOPMENT OF OSCILLATING CONTRACTIONS AND ACETYLCHOLINE RECEPTORS IN CHICKEN EMBRYONIC SMOOTH MUSCLE. M.R. James-Kracke* and I.K. Bozoky* (SPON: J. Bowen). University of Missouri-Columbia, 65212.

Large rhythmic oscillating contractions of the circular smooth muscle of the embryonic intestine (CSM-EI) begin 5 min after stimulation by carbachol during the tonic phase. These oscillations are very apparent in chicken CSM-EI between 11 and 15 days of development and less apparent in earlier and later stages. The peaks of $[Ca^{2+}]_i$ during these tonic waves are greater between 11-15d whereas the peak phasic $[Ca^{2+}]_i$ is greater before and after this developmental stage. The magnitude of phasic contraction and the number of muscarinic receptors per cell increase over 11-15d. Phorbol myristate acetate (PMA), which stimulates protein kinase C (PKC), accentuates the oscillating changes in $[Ca^{2+}]_i$, pH_i and contraction (spontaneous and carbachol induced) in 11-15d muscles but has less effect on younger and older embryos. We are attempting to determine whether stimulation of PKC by PMA (or diacylglycerol) during muscarinic receptor activation alters the Ca-H, Na-H, Ca (ATP driven) pump and/or Na-Ca exchange in opposing rhythmical ways to cause these oscillations. The CSM-EI is a good model system to study regulation of spontaneous activity. Other aspects of e-c coupling are also being studied as they develop. Supported by the NIH 5R23AR35435-03 and the National American Heart Association.

14.12

FORSKOLIN AND CYCLIC AMP ANALOGUES POTENTIATE ATP-INDUCED Ca^{2+} TRANSIENTS IN MYOCYTES. Zheng J-S*, M.B. De Young*, M. N. Levy and A. Scarpa Dept. of Physiology and Biophysics, Case Western Reserve University, Cleveland, OH 44106.

It has been recently shown by this laboratory that extracellular ATP in micromolar concentrations produces in isolated myocytes a rapid transient in intracellular Ca^{2+} concentrations and that this effect is potentiated by pretreatment with norepinephrine (NE). The mechanism by which NE potentiates the ATP-induced Ca^{2+} transient has been investigated using Fura2 loaded rat myocytes in suspension. Pretreatment with micromolar concentration of forskolin (an activator of adenylate cyclase) potentiates the ATP-induced Ca^{2+}-transient. Permeable cAMP analogues such as 8-(4-chlorophenyl)-cAMP (500uM), dibutyryl cAMP (500uM) and 8-bromo-cAMP (500uM), also enhance ATP-induced Ca^{2+} responses. However cAMP, dibutyryl-cGMP and 8-bromo-cGMP do not modify ATP-Ca^{2+} response. The potency order of these cAMP analogues is: 8-(4-chlorophenyl)-cAMP > dibutyryl cAMP = 8-bromo-cAMP > cAMP. Forskolin, NE and 8-(4-chlorophenyl)-cAMP shift the ATP dose response curve to the left. Pretreatment with isomethyl-butylxanthine (IBMX), a phosphodiesterase inhibitor, potentiates the ATP-induced Ca^{2+} response. IBMX also synergizes with forskolin, 8-(4-chlorophenyl)-cAMP and NE. These results suggest that adenylate cyclase is the second messenger system involved in noradrenergic potentiation of the intracellular calcium mobilizable upon addition of extracellular ATP. Cholera toxin has potentiatory effects on the ATP-Ca^{2+} response. It also synergizes with forskolin and IBMX but not with NE. These results are consistent with a G-protein involvement in potentiation of the ATP-induced Ca^{2+} response. Supported by NIH Grants HL15758 and HL18708.

14.13

ROLE OF PROTEIN KINASE C AND INOSITOL TRISPHOSPHATES (IP3) IN CONTRACTION OF CAT ESOPHAGUS AND LOWER ESOPHAGEAL SPHINCTER. *C. Hillemeier, P. Biancani, J. Marshall, *D. Ar, *K. Balazovich. Univ. of Michigan, Ann Arbor, MI 48109 and Brown University, Rhode Island Hospital, Providence, RI 02903.

In strips and isolated smooth muscle cells we have previously shown that esophageal contraction in response to Acetylcholine (Ach) is mediated by influx of extracellular calcium, whereas LES contraction and tone depend on release of calcium from intracellular stores. We now examine the intracellular messengers responsible for LES and esophageal contraction. 1) After permeabilization with saponin and incubation in Ca^{++}-free "cytosolic" medium, LES but not esophageal cells contract in response to inositol trisphosphate (IP3), an inositol metabolite that mediates release of calcium from the intracellular stores. 2) After loading the LES and esophagus with myo-(2-^{3}H)-inositol, resting levels of IP3, measured by an ion exchange chromatography (Dowex) and HPLC, are at least 3 times greater in the LES than in the esophagus. 3) The putative calmodulin antagonists triflouprizine, W7 and CGS9343B antagonize contraction of LES cells in response to Ach, but have no effect on the esophagus. 4) Protein kinase C (PKC) activity, measured by a histone phosphorylation assay, was higher in the particulate fraction of the unstimulated LES than in the esophagus ($P<0.05$). The particulate fraction is thought to be correlated with the activated enzyme and functionally activated cells. 5) In the esophagus, but not in the LES Ach induced contraction was associated with an increase in the particulate fraction of PKC. The contraction was blocked by the PKC antagonist H-7.

These data are consistent with the view that LES tone and response to Ach depend on release of intracellular calcium through an IP3-dependent pathway, whereas the esophageal contraction requires influx of extracellular calcium and activation of a PKC-dependent pathway.

14.14

CYTOSOLIC HEPARIN INHIBITS Ca^{2+} RELEASE COMPONENT OF PHARMACOMECHANICAL COUPLING IN SMOOTH MUSCLE. S. Kobayashi*, T. Kitazawa*, A.V. Somlyo, and A.P. Somlyo. Univ. of Virginia, Charlottesville, VA 22908

In order to test the physiological significance of inositol 1,4,5-trisphosphate ($InsP_3$) in pharmacomechanical coupling, we have utilized two near-physiological systems, in which relatively high molecular weight solutes can be applied intracellularly and receptor coupling is retained: β-escin-permeabilization and reversible permeabilization. In smooth muscles permeabilized with β-escin, α_1-adrenergic (phenylephrine) and muscarinic (carbachol) agonists, as well as caffeine and $InsP_3$, caused contractions mediated by Ca^{2+} release. Heparin (Mr = about 5,000), a blocker of $InsP_3$-binding to its receptor and a specific inhibitor of $InsP_3$-induced Ca^{2+} release in smooth muscles (Kobayashi et al., Biochem. Biophys. Res. Commun. 153:625-631, 1988), inhibited the responses to the agonists and to $InsP_3$, but not those to caffeine, nor did it block the enhanced Ca^{2+} sensitivity induced by agonists. In reversibly permeabilized ileum smooth muscle cells, loaded with Fura-2 acid and heparin, the intracellular heparin inhibited Ca^{2+} release and contractions induced by carbachol in Ca^{2+}-free, high K^+ solution. Heparin did not inhibit the high K^+-contractions (with 1.2mM Ca^{2+}), and had no significant inhibitory effects on carbachol-induced responses in the presence of extracellular Ca^{2+}. These results, obtained under near-physiological conditions, support the conclusion that $InsP_3$ is the major physiological messenger of the Ca^{2+} release, but not the Ca^{2+} influx, component of pharmacomechanical coupling.

This work was supported by National Institutes of Health grant HL15835.

14.15

PHORBOL ESTER POTENTIATES BETA-ADRENERGIC RELAXATION OF RABBIT AIRWAY SMOOTH MUSCLE. C.M. Schramm* and M.M. Grunstein. Univ. of Pennsylvania, Philadelphia, PA 19104.

We have recently demonstrated (J. Appl. Physiol 66:1935, 1989) that activation of protein kinase C (PK-C) with phorbol esters augments Na^+-K^+ pump activity in rabbit airway smooth muscle (ASM). Since airway relaxation with beta-adrenergic agonists has been associated with enhanced activity of the Na^+-K^+ pump, the present study evaluated whether PK-C activation with 12-deoxyphorbol 13-isobutyrate (DPB) modulates ASM relaxant responses to beta-adrenergic stimulation with isoproterenol (ISO). Isometric tension was monitored in ASM segments mounted in organ baths containing aerated, modified Krebs-Ringer solution. During sustained half-maximal contractions with acetylcholine (ACH), the tissues were relaxed with cumulative addition of ISO (10^{-9} to 10^{-4} M). Tissues of similar ACH and ISO responsiveness were then paired into 4 groups: control (n=7); DPB (10^{-7} M; n=7); ouabain (10^{-6} M; n=5); and ouabain plus DPB (n=5). Thereafter, the ASM relaxant responses to ISO were repeated. Relative to control tissues, we found that: 1) DPB potentiated ASM relaxation to all concentrations of ISO; 2) ouabain pretreatment markedly blunted ASM relaxant responses to ISO; and 3) ouabain abolished the above potentiating effect of DPB on ISO responsiveness. Collectively, these findings demonstrate that PK-C activation augments ASM relaxation to beta-adrenergic stimulation, and the latter effect is dependent on the integrity of the airway Na^+-K^+ pump.

14.16

ACTIVATION OF ARTERIAL MUSCLE BY FLUORIDE. Paul H. Ratz, Adrienne Boothe, and Jeffrey Weiseman. Eastern Virginia Medical School, Norfolk, VA 23501.

Aluminum fluoride (AlF: 10 mM NaF, 20 uM $AlCl_3$) produced strong contractions (1.45 ± 0.25 S_o) in a Ca^{2+}-containing solution (CCS), and weak, sustained contractions (0.19 ± 0.03 S_o) in a Ca^{2+}-free solution (CFS). In CCS, force was not sustained, but declined slowly to 0.5-fold maximum within 2 hrs. NaF alone produced contractions only in CCS (1.11 ± 0.04 S_o). Contractions in CFS were not blocked by phorbol dibutyrate. In CCS, AlF increased the extent of myosin phosphorylation (12% basal, 38 ± 4% AlF). Inositol phosphate production was not increased by AlF in CFS. Force redevelopment following quick-releases suggested that AlF in CFS activated crossbridge cycling. AlF contractions in CCS were completely relaxed by the kinase inhibitor, H7 and the calmodulin inhibitor, W7, but not completely relaxed by the Ca^{2+} channel blocker, nifedipine. The order of potency for Ca^{2+} dose-response curves in the presence of different agonists was: AlF > NaF > histamine > phenylephrine > KCl. These data suggest that NaF transiently activated Ca^{2+} channels, and AlF produced additional extracellular Ca^{2+}-independent activation of force. Support: AHA and VA Affiliate.

14.17

EFFECTS OF GTPγS AND NEOMYCIN ON INOSITOL LIPIDS IN RAT TAIL ARTERY. Edward F. LaBelle* and Bonnie Murray* (SPON: R.H. Cox). Graduate Hospital, Phila., PA 19146

The metabolism of inositol lipid was investigated in rings of rat tail artery in order to increase our understanding of the molecular mechanisms of norepinephrine (NE)- and vasopressin (AVP)-stimulated vascular contraction. The rings were preincubated for 3 hrs with [^{3}H]inositol to label the inositol lipids and then treated with LiCl (10 mM) either with or without NE or AVP before being extracted with trichloracetic acid to release IP, IP_2, and IP_3. The inositol phosphates were separated by Dowex ion-exchange chromatography. Both NE and AVP increased the production of IP, IP_2, and IP_3 within the cells of rat tail artery. When the tail artery rings were prelabeled with [^{3}H]inositol and then permeabilized by treatment with EGTA and ATP, NE and AVP could still stimulate the release of IP, IP_2, and IP_3 from lipid within the tissue, and now the inositol phosphates could leave the permeable cells and accumulate in the external solution. GTPγS (10^{-4} M) could also stimulate the production of IP, IP_2, and IP_3 within the permeable rings, and GTPγS plus NE stimulated inositol phosphate production within the rings in a process that was non-additive. This indicated that a G protein might be involved in mediating the effects of hormone receptors on inositol lipid breakdown in vascular smooth muscle. Neomycin blocked the AVP-stimulated release of inositol phosphates in tail artery rings. Neomycin also blocked the AVP-stimulated contractions of tail artery rings at sub-maximal concentrations of AVP (10^{-8} - 10^{-6} M). Neomycin blocked contractions induced by K^+ as well, perhaps as a result of direct inhibitory effects on Ca^{+2} mobilization. (Supported by NIH Grant HL37413.)

14.18

EFFLUX OF CYCLIC AMP IS REGULATED BY OCCUPANCY OF THE ADENOSINE RECEPTOR IN CULTURED ARTERIAL SMOOTH MUSCLE CELLS. Linda L. Slakey*, Ellen S. Dickinson*, Thomas F. Fehr*, and Samuel J. Goldman*(Spon. D.N. Spinelli). Univ. of Massachusetts, Amherst, MA 01003

Efflux of cAMP from stimulated cells has been reported for several cell types (Barber and Butcher, Adv.Cyc.Nuc.Res. 15,119,*1983*). When pig aortic smooth muscle cells are treated with adenosine, intracellular cAMP rises, and cAMP accumulates in the incubation medium. No ATP leaks from the cells under the conditions of the experiment. Efflux of cAMP is sharply temperature dependent, falling to below measurable levels at 15°C. Efflux stops abruptly when agonist is removed. Cellular cAMP also falls, but is still in a range which supports efflux in the presence of agonist. At cellular cAMP levels below 100 pmol/10^6 cells, efflux displays pseudo first order dependence on cellular cAMP. The apparent first order rate constant for efflux increases in a dose-dependent manner in response to adenosine or 5-(N-ethyl)-carboxamideadenosine (NECA). The EC50 of the efflux rate constant is 12 μM for adenosine and 5 μM for NECA. Efflux is not inhibited by H8 (N-[2-(methylamino)ethyl]-5-isoquinolinesulfonamide), an inhibitor of cAMP dependent protein kinase. Treatment of cells with either cholera toxin or forskolin alone also causes efflux together with a rise in cellular cAMP. The data are consistent with a model in which cAMP efflux is linked to activation of adenylyl cyclase in this cell type. Support: NIH HL 38130.

14.19

SUBSTANCE P ACTIVATES A RECEPTOR-OPERATED CA CHANNEL IN COLONIC SMOOTH MUSCLE. E.A. Mayer, A. Kodner, D.D.F. Loo, S. Supplisson, G. Sachs. Dept. of Medicine, Harbor-UCLA Medical Center and Dept. of Physiology, UCLA, Los Angeles, Ca. 90024.

The existence of a receptor-operated Ca^{2+} permeable ion channel in gastrointestinal muscle which is activated by muscarinic agonists has been postulated. To demonstrate the existence of such a receptor-operated channel, we studied single channel and whole cell currents in freshly dispersed myocytes from the longitudinal muscle layer of the rabbit colon using the patch clamp technique. In whole cell recordings (bath solution: NaCl Ringer; pipette solution: 140 mM CsCl, 2 ATP, 2 EGTA) , the NK-1 receptor agonist substance P methylester (SPME; 10^{-13} M - 10^{-11} M)) stimulated an inward current at the holding potential of -50 mV which showed poor selectivity between Ca^{2+}, Ba^{2+},Na^{+},K^{+},Cs^{+} and Cl^{-}. When patches were excised into the outside out configuration, SPME dose-dependently increased the open probability of ion channels with a conductance of 2 pS, which showed poor selectivity between Ca^{2+} and Na^{+}. Activation in excised patches was not dependent on cytosolic Ca^{2+}, ATP, or GTP. Channels were inhibited by Zn^{2+} and La^{3+}, but not by dihydropyridines. In the cell-attached recording mode, addition of SPME to the bath had no effect on channel openings. These results suggest: 1. Substance P allows Na^{+} and Ca^{2+} influx by activation of a small conductance, ion channel coupled to high affinity NK-1 receptors, 2. Receptor channel coupling does not involve $[Ca^{2+}]_i$, G proteins or channel phosphorylation.

HORMONAL REGULATION

15.1

APIII INTERACTIONS WITH ENDOTHELIN-INDUCED CONTRACTIONS IN RABBIT AORTA. E. I. Novosad* and T. J. Opgenorth. Abbott Laboratories, Abbott Park, IL 60064.

The identification of the vasoactive peptides atrial natriuretic factor (ANF) and endothelin (ET) has prompted much investigation into the mechanisms of vascular tone maintenance and blood pressure regulation. ANF exerts potent vasorelaxant effects while ET induces potent and long-lasting vasoconstriction. We investigated the effects of the ANF analog APIII and ET (human ET-1) on rabbit aortic rings (RAR) at a baseline tension of 2 g (Krebs-Henseleit buffer, 2.5 mM Ca^{2+}, 37°C and pH 7.4). ET contracted in a dose-dependent manner RAR with an EC50 of 9.54 ± 0.12 (-log M) for 7.21 ± 0.28 g maximal effect (N=11). ET potency was not affected when initial dose-response curve (DRC) concentrations varied from 1E-13 to 1E-8 M, however, with initial DRC concentrations of 1E-9 M or greater, maximum contraction was reached progressively sooner. Initial DRC concentrations greater than 1E-9 M produced a transient contraction; the "long-lasting" effect normally associated with ET contraction was observed only at or near EC50 concentrations. Addition of APIII (3E-8, -7, or -6 M) 15 min prior to initiation of the ET DRC did not affect ET potency or efficacy. In a separate set of experiments, APIII completely relaxed 1E-9 M ET contracted RAR with an IC50 of 9.66 ± 0.06 (N=4). In conclusion, APIII appears to be more selective for relaxation of vascular smooth muscle with ET-elevated tone than for antagonism of the ET dose-response relationship in RAR. These data suggest that ANF-induced relaxation and ET-induced contraction participate in an intracellular homeostatic relationship which is influenced by the degree of vascular tone.

15.2

ARTERIOLAR CONSTRICTION TO ANGIOTENSIN II IS MEDIATED BY CALMODULIN-DEPENDENT MYOSIN LIGHT CHAIN KINASE AND PROTEIN KINASE C. John T. Fleming and Sharon R. Inman*, University of Louisville, KY 40292.

In the present study we determined if the constriction of small arterioles to angiotensin II (Ang II) is mediated by activation of calmodulin-dependent, myosin light chain kinase and protein kinase C. The right cremaster muscle of male Sprague Dawley rats (140-200g), anesthetized with Inactin, was exteriorized in a temperature and pH controlled bath. The diameters of third order arterioles (14-24 μm) were measured before and after the addition of Ang II (10^{-7}M bath concentration). After Ang II washout the calmodulin inhibitor (calmidazolium (calmid), 10^{-4}M) was added to the bath alone or 10 minutes following the application of the protein kinase C inhibitor (H7, 10^{-4}M). Thirty to 40 minutes later Ang II was reapplied to the bath (10^{-7}M). Arteriolar diameter changes (expressed as % of the control diameter; control = 100%) are given below (x±SEM):

N	AngII	Calmid	H7 + Calmid	AngII After Inhibitor(s)
4	29±14%	150±14%	---	53±27%
4	47±14%	---	233±47%	219±41%

Though the calmodulin inhibitor dilated the arterioles, it alone did not prevent the constriction to Ang II. The combined inhibition of calmodulin and protein kinase C abolished the constrictor response. These data suggest that Ang II induced arteriolar constriction is not mediated solely by a calmodulin pathway but likely also involves protein kinase C.

15.3

THE DISULFIDE BONDED RING OF ISO-rANP, UNLIKE THE RING OF rANP, HAS CIRCULATORY AND SMOOTH MUSCLE RELAXANT ACTIVITY. D.B. Jennings, I. Sarda and T.G. Flynn. Depts. Physiology and Biochemistry, Queen's University, Kingston, Canada, K7L 3N6.

We recently reported a second peptide [iso-rANP(1-45)] from rat atria with circulatory and renal activities (Flynn et al.. Physiologist 31:A1, 1988). The disulfide ring portion of this new peptide [iso-rANP(23-39)] has 70% homology with rANP(105-121), but the amino and carboxyl termini of iso-rANP(1-45) and rANP(99-126) lack homology.

In contrast to rANP(105-121) which lacks biological activity, injection of iso-rANP(23-39) into anesthetised rats resulted in transient decreases in mean arterial pressure (MAP) of 14.6% and 21.7% at doses of 1.5 and 3.0 nmols. Heart rate (HR) also decreased by 6%; there were also small inconsistent increases in water and Na+ excretion from the kidney with iso-rANP(23-39) at both doses, but not with rANP(105-121). The sustained effects of iso-rANP(1-45) in lowering MAP and HR were not present with the ring alone but it is responsible for the direct circulatory effects of iso-rANP(1-45) in vagally chemodeafferented rats. Iso-rANP(23-39) also caused relaxation of rabbit aortic rings, with or without endothelial cells, preconstricted with phenylephrine. Replacing the arginine in the ring at position 36 with the glycine at the comparable position of the ring of rANP did not affect either the circulatory or smooth muscle activities of iso-rANP(23-39). Supported by Queen's University and the Medical Research Council.

16.1

COMPARISON OF THE EFFECTS OF AORTIC AND SINOAORTIC BARODENERVATION ON MEAN ARTERIAL PRESSURE (MAP) AND URINARY SODIUM EXCRETION (UNaV) IN CONSCIOUS RATS.

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To compare the effects of partial (aortic; ABD, N=7) and complete (sinoaortic; SAD, N=5) arterial barodenervation on MAP regulation, MAP, lability of MAP, and UNaV were measured for two control days (C1-C2) before and seven experimental days (E1-E7) after denervation. MAP and the standard deviation of MAP (MAP-SD) were obtained by daily 30 minute computerized recordings. The MAP-SD was used as an index of MAP lability. Simultaneous measurements of daily UNaV were taken while the rats were maintained on a fixed Na intake (3.5 meq/day). The hypertensive response to barodenervation on day E1 was similar in both ABD (+20.4 ± 4.0 mmHg) and SAD (+17.8 ± 5.2 mmHg) rats. MAP returned to control levels by day E3 in both groups. Overall, the MAP-SD increased 70% after ABD and 140% after SAD. In both groups UNaV increased on E1 but returned to control by E2. We conclude that 1) the hypertension produced by ABD and SAD was similar in magnitude, but was not maintained beyond three days after barodenervation in either group, 2) although MAP was similar in both groups, the lability of MAP was higher after SAD and 3) normalization of MAP after ABD and SAD may be dependent on renal Na excretion.

16.2

CAROTID BARORECEPTOR GAIN IS AFFECTED BY WHOLE BODY AUTOREGULATION IN DOGS.

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Five chloralose anesthetized, closed-chest dogs (25-37kg) were used in both open- and closed-loop experiments to determine carotid baroreceptor gain. Aortic and cardiopulmonary baroreceptor input to the system was minimized by vagotomy. The carotid sinuses were isolated and perfused using a pressurized blood reservoir for the open-loop experiments. Carotid sinus pressures were altered in step-wise fashion and were correlated with corresponding changes in ascending aorta pressure. Closed-loop (intact) conditions were evaluated by restoring the connection between the carotid sinuses and the systemic circulation and evaluating step reductions in cardiac output by postcaval obstruction. Systemic autoregulation was assessed by maintaining carotid sinus pressure constant and reducing cardiac output in steps as previously described. In all cases vena caval occlusions were released and baseline recordings repeated between each new level of caval occlusion and cardiac output reduction. We found that when the influence of autoregulation was ignored baroreflex open-loop gain, as estimated from the closed-loop method, was underestimated by an average of 0.88±0.48. By including the effects of whole body autoregulation the open-loop gains estimated by the same method averaged 2.23±0.84. This agreed with the results obtained from the open-loop experiments in the same dogs where the absolute gains were 2.27±1.01. Baroreflex resistance gains, as computed from our model, were 0.32±0.15 min/l and 0.83±0.25 min/l in the absence and in the presence of autoregulation, respectively.

This work supported, in part, by NATO Scientific Affairs Division Grant #04-0054-87 and the italian MPI.

16.3

CARDIAC OUTPUT AND THE BLOOD PRESSURE INCREASE IN DEOXYCORTICOSTERONE-ACETATE (DOCA) - SALT SENSITIVE HYPERTENSION AFTER NICOTINE INFUSION.

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Cigarette smoking exacerbates malignant hypertension in human patients (Isles et al. Brit. Med. J. 1:599, 1979). We have tested the hypothesis that the nicotine of cigarettes exaggerates the blood pressure increase in DOCA-salt sensitive hypertensive rats. DOCA pellets were implanted subcutaneously into uninephrectomized rats and the animals were placed on a high sodium chloride diet with sham (nicotine) infusion (Group 1) or nicotine infusion (Group 2) via osmotic minipump beginning two weeks after DOCA implant. Groups 3 and 4 included sham (DOCA) implant and normal salt diet with nicotine infusion (Group 3) or sham (nicotine) infusion (Group 4). Tail-cuff blood pressures were recorded for five weeks and the animals were then subjected to a terminal experiment to determine arterial blood pressure and cardiac output. The blood pressures of Group 2 rats were significantly greater than Group 1 at 1.5 to 3.5 weeks after nicotine infusion ($p<.025$). Group 3 rats demonstrated no increase in blood pressure compared to Group 4 controls. Cardiac output of Group 2 rats was significantly greater than that of Group 1 rats at 2.5 weeks after nicotine infusion ($p<.01$). Our conclusion is that the increase in blood pressure in the nicotine treated animals (Group 2) was due in part to an increase in cardiac output. (Supported by KY Tobacco Health & Research Institute Grant).

16.4

ADRENAL EPINEPHRINE IS NOT ESSENTIAL FOR THE DEVELOPMENT OF HYPERTENSION IN THE DAHL SALT-SENSITIVE RAT.

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It has been hypothesized that epinephrine (E) of adrenal origin may play an important role in the initiation of several forms of hypertension. In the present experiments we tested the hypothesis that SK&F 29,661, an inhibitor of adrenal (but not CNS) PNMT, would prevent or attenuate the development of salt-induced hypertension in the DS rat. Male DS rats were maintained on a 0.45% NaCl diet, and were treated orally with SK&F 29,661 at doses of 1-2 g/kg/day or with distilled water vehicle (10 ml/kg/day), starting at 3-4 weeks of age. After at least 18 days of treatment, animals were instrumented with a femoral arterial catheter which permitted direct measurement of mean arterial pressure (MAP). Three days after surgery the animals were placed on a 7% NaCl diet and MAP was measured daily for the next 3 weeks. SK&F 29,661 treatment was effective in reducing adrenal E synthesis and release, as judged by a 78% reduction in plasma E following acute footshock and an 81% reduction in adrenal E content, compared to control animals. However, SK&F 29,661 treatment did not alter either the time course or the magnitude of the salt-induced increases in MAP in DS rats. MAP increased by 25 ± 5 mmHg in vehicle-treated animals and by 32 ± 5 mmHg in SK&F-treated animals over the three weeks of 7% NaCl diet. We conclude that adrenal E is not required for the development of salt-sensitive hypertension in the DS rat. (Supported by NIH HL-37753).

16.5

CARDIOVASCULAR AND METABOLIC EFFECTS OF I.V. INFUSIONS OF ISO-rANP(17-45) IN AWAKE DOGS.

P.J. Ohtake, J.C. McKirdy, T.G. Flynn and D.B. Jennings. Depts. Physiology and Biochemistry, Queen's University, Kingston, Canada, K7L 3N6.

We reported a second peptide [iso-rANP(1-45)] extracted from rat hearts. Both iso-rANP(1-45) and the iso-rANP(17-45) portion, analagous to rANP(99-126), have similar circulatory and renal activities to rANP(19-126) (Jennings et al., Physiologist 31:A1, 1988). Iso-rANP(17-45) was infused into the right ventricle of 6 awake dogs for sequential 20 min periods at doses of 40, 80 and 160 ng/kg/min. The most striking finding was a progressive increase in oxygen consumption ($\dot{V}O_2$) (+13% and +35%) and increased extraction of arterial oxygen (+36% and +42%) at 40 and 80 ng/kg/min infusion rates, respectively. Comparable infusions of saline or of rANP(99-126) (80 ng/kg/min) over 40 min in a comparable series of experiments had no significant effect on $\dot{V}O_2$. These metabolic effects of iso-rANP(17-45) preceded circulatory changes. Average cardiac output and peripheral resistance were not measurably affected throughout. Mean and diastolic pressures did not consistently decrease until infusion of the 160 ng/kg/min dose, although arterial pulse pressure decreased by the 80 ng/kg/min dose. Progressive decreases in paw skin temperature suggest redistribution of blood flow to maintain MAP. At low doses, therefore, a primary effect of iso-rANP(17-45) appears to be an increase in metabolism. Supported by Queen's University and MRC.

16.6

CHRONIC ORAL TREATMENT WITH 6-IODO-AMILORIDE (6IA) OF RATS WITH 1-KIDNEY, 1 CLIP (1-K, 1-C) HYPERTENSION (HT).

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We have shown that 6IA, a Na channel blocker, produces vasodilation when infused intraarterially in the dog forelimb. Intra-venous (IV) infusion of 6IA in normal dogs and rats produces hypotension. IV infusion of 6IA also produces a sustained decrease in BP in genetic models of HT, namely SHR and Dahl salt-sensitive (DS) rats, models believed to have increased vascular smooth muscle cell (VSMC) Na permeability. However, 6IA has only a transient BP lowering effect in renal models of HT, namely 1-K,1-C and reduced renal mass saline HT in rats, models thought to have normal VSMC Na permeability. Furthermore, chronic oral administration of 6IA in SHR and DS rats produces a progressive decrease in BP. We have now examined the effect of oral administration of 6IA on BP in 1-K, 1-C HT in rats. After surgery, 1-K, 1-C rats were immediately and randomly divided into experimental (E) and control (C) groups and placed on treatment or sham treatment. E rats drank tap water containing 6IA (7.6 mg/100 ml) for 5 weeks. The C rats drank tap water for the same period. 6IA treatment had no effect on the development of HT in E rats; BP increased progressively and equally in E and C groups. 6IA also had no effect on urinary excretion of urine volume, Na or K. Additionally, plasma osmolality, and the concentrations of Na, K, Ca, Mg, Cl, creatinine and BUN were also not different in E and C groups. These results show that 6IA though a potent antihypertensive agent in the genetic models of HT, is not an effective antihypertensive agent in renal models of HT in rats.

16.7

Calcium and Cyclosporin A -induced potentiation of vascular contractility.
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Cyclosporin A (CsA) therapy is associated with increased incidence of hypertension. CsA in vitro augments the contractile action of several vasoconstrictors suggesting an effect on a common mechanism. In the isolated perfused rat mesenteric vascular bed we found that CsA applied either in vivo (10 mg/kg/7 days) or in vitro (0.083-8.3 μM) increases the contractile action of NE and K^+ (125-152% and 118-145% of control, respectively $p<0.001$) in a dose dependent manner. This effect of CsA was not observed when the mesenteric preparation was treated with CsA in Ca^{2+} free solution, indicating that the described effect of CsA is absolutely dependent on extracellular Ca^{2+} Neither verapamil nor nifedipine however, prevented the increment in NE action, suggesting increased Ca^{2+} transport across non-voltage operated channels. Increased contractile responses to NE were also observed when the mesenteric preparation was treated with CsA in normal Kreb's buffer, and then equilibrated in Ca^{2+} free solution (+EGTA 100 μM) for 30 min (135% of the control $p<0.001$); suggesting that CsA increases the content and release of Ca^{2+} from intracellular pools. Support for this finding was found in preparations perfused with Ca^{2+} free solution, in which a significant reduction (80%) of the CsA effect was obtained with Dantrolene (10^{-4} M) an intracellular Ca^{2+} blocker. This suggests that the sarcoplasmic Ca^{2+} pool or the Ca^{2+} loosely bound to the cell membrane may be increased by CsA. In conclusion our experiments show that CsA potentiation of contractility is dependent on extracellular Ca^{2+}, and that increased intracellular Ca^{2+} pools significantly contribute to this effect. The potentiation of the contractile action of endogenous agonists like catecholamines may play a role in CsA-induced hypertension. [NIH HL40069]

CARDIOVASCULAR DYNAMICS

17.1

CARDIAC RECEPTORS MEDIATE THE PHENYL DIGUANIDE DEPRESSOR RESPONSE IN THE RABBIT.
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Phenyl diguanide (PDG) has been described as a lung receptor stimulant (Dawes, et al. J Physiol. 115:258, 1951). However, Bell, et al. (Proc. IUPS 1989) have shown that after chronic lung denervation, the Hering-Breuer reflex is abolished, but the PDG depressor response remains. It was concluded that the PDG depressor response was not mediated by lung receptors. This study was designed to determine if: 1) cardiac receptors mediate the PDG depressor response, and 2) if this response is mediated via vagal afferents alone. Five NZW rabbits were anesthetized with 30 mg/kg thiamylol (IV) and halothane, intubuted and artificially respirated. Arterial pressure (AP) was obtained via an ear artery, and heart rate (HR) was derived from the AP. Both vagi were isolated cervically and a cathether was placed intrapericardially through a left thoracotomy. Responses to PDG (60 mg/kg) were obtained before and during intrapericardial procaine (5%), (used to block afferent and efferent cardiac nerves). Thirty minutes after procaine infusion, the PDG depressor response returned. A bilateral vagotomy was then performed and the PDG infusion repeated. Control PDG infusions produced a transient hypotension (-16.2±3.8 mmHg, S.D.) and bradycardia (-22.8±13.9 b/min). This depressor response was abolished by procaine (AP and HR changes were 0.0±1.4 mmHg and 2.8±4.6 b/min, respectively). After the PDG depressor response returned, bilateral vagotomy abolished the PDG response in three rabbits and attenuated it in two. These results indicate that the PDG depressor response is mediated through cardiac receptors with either vagal, or vagal and sympathetic afferents. Supp.by WHA.

17.2

CHRONIC VENTRICULAR SYMPATHECTOMY AND SUPERSENSITIVITY.
Marilyn A. Brandt, Patricia A. Gwirtz, Carl E. Jones, Howard J. Mass and Melissa L. Hamrick. Texas College of Osteopathic Medicine. Fort Worth, TX 76107.

Due to the increased frequency of cardiac transplantation, it is important to understand the responses of the chronically sympathectomized heart to the adrenergic neurotransmitter norepinephrine (NE). The present study examined the time-dependent effects of surgical ventricular sympathectomy on myocardial and coronary supersensitivity to NE. In 4 sympathectomized and 8 sham-operated control hearts, dP/dt_{max}, rate of posterior segmental shortening (dL/dt_{max}), and circumflex flow velocity were measured 2, 4 and 8 wks after surgery, before and after NE administration. NE was administered in doses of 0.01 - 0.50 μg into the circumflex artery of conscious dogs. Elevated responses in the sympathectomized hearts were most evident after 2 wks compared to controls, where 0.50 μg of NE increased dP/dt_{max} by 74% (vs 50%) and dL/dt_{max} by 148% (vs 106%). Because of the increased myocardial response, coronary functional hyperemia increased by 108% (vs 56%). Increased responses were similarly observed in sympathectomized hearts at the lower doses of NE compared to controls. The myocardial supersensitivity was reduced but still evident after 4 and 8 wks. Interestingly, at no time was the coronary constrictor response to NE different between sympathectomized and control hearts. We conclude that a transient myocardial supersensitivity to NE is present after ventricular sympathectomy, but that a coronary supersensitivity does not occur. (Supported by HL-31144 and HL-34172.)

17.3

COMBINED CARDIOTONICS: DOPAMINE MECHANISMS.
H. Rambaran*, J. Bianchi, J. Gallaher*, C.A. McClernan*. Deborah Research Institute, Browns Mills, NJ 08015-1799

The study was designed to determine effect and mechanism of action of combined cardiotonics. Guinea pig left atrial trabeculae were used for isometric twitch studies at Lmax. Twitch contractions were electrically stimulated (5 ms, 2x threshold, 0.5 Hz). Ventricular tissue was homogenized in Tris maleate buffer (80 mM, pH 7.2) and differential centrifugation was used to produce a fraction enriched in sarcolemmal membranes. Radioligand binding studies were performed with dopamine and dihydroalprenolol as substrates, and dobutamine, haloperidol, and propranolol as competitors. Dopamine did not augment twitch force when given with 1 uM isoproterenol (compared to isoproterenol alone) and failed to reverse propranolol-induced negative inotropy. Dopamine binding to sarcolemmal membranes was saturating and inhibited by 10 uM dobutamine (33±9% of control; n=6), 10 uM propranolol (28±7% of control; n=6) but was not inhibited by 1mM-0.1 uM haloperidol (107±12% of control; n=3). Dihydroalprenolol binding was saturable and was inhibited by 10 uM propranolol (39±8% of control; n=4), 10 uM dopamine (72±7% of control; n=3), 10uM dobutamine (61±10 of control; n=4), and 10 uM haloperidol (62±8% of control; n=3). The results suggest that dopamine and its analogs exert their pharmacological effects in the heart primarily through beta-adrenoceptors, as demonstrated by binding data. Supported by a Deborah Research Grant.

17.4

EFFECT OF BETA-ADRENERGIC BLOCKADE ON REGIONAL CAPACITANCE AND UNSTRESSED VOLUME IN DOGS DURING HEAT STRESS.
A. Deschamps, R. Naamani, I. Shrier, and S. Magder. McGill University, Royal Victoria Hospital, Intensive Care Unit, Montreal, Canada.

We tested the hypothesis that beta-adrenergic stimulation predominates in the decrease in vascular capacity during heat stress. Pressure-volume (P-V) curves of the peripheral (PER) and splanchnic (SPL) regions were studied in 4 alpha-chloralose anaesthetized dogs on circulatory bypass by alternating stop flow pressure measurements with step increases in venous outflow pressure. Cardiac output was maintained constant and regional blood volumes were obtained by Dye dilution technique and mean transit time. Extrapolation of the P-V curve to zero pressure was used to obtain unstressed volume. Heat stress (H, Tc = 42oC) was used to initiate a decrease in capacitance and propranolol (Pro, 0.3 mg/kg) was infused to estimate the contribution of beta stimulation to this decrease. Heart rate decreased from 170 ± 13.2 to 145 ± 12.6 beats/min with Pro (P 0.005). The total blood volume of the SPL region was not altered by Pro (22.8 ± 1.0 ml/kg for H and 23.2 ± 0.8 ml/kg for Pro); neither was unstressed volume (11.0 ± 1.2 and 12.8 ± 0.9 ml/kg). The same was true for PER total blood volume (13.2 ± 1.5 and 14.0 ± 1.5 ml/kg) and unstressed volume (9.2 ± 1.6 and 11.4 ± 1.6 ml/kg for PER). Beta-blockade did not affect the venous compliance of either SPL or PER. We therefore conclude that beta-adrenergic stimulation does not play a role in the mobilization of unstressed volume during heat stress.

17.5

EARLY ATHEROSCEROSIS INDUCED CHANGES IN ARTERIAL HISTOMORPHOLOGY DO NOT RESULT IN PREDICTABLE CORRESPONDING CHANGES IN PULSATILE PRESSURE/FLOW RELATIONSHIP. D.R. Gross, M.S. Cannon*, L.J. Mulligan, J.M. Gross* and S.M. Hays*, Veterinary Physiology and Pharmacology (D.R. Gross, Mulligan and Hays), Medical Anatomy (Cannon), Texas A&M University, College Station, TX 77843 and Cardiovascular Flow Dynamics Lab. (J.M. Gross) University of Houston, Houston, TX 77004

We conducted three series of experiments to: 1) Demonstrate that known changes in compliance just distal to the inlet of a well defined system could be detected using an analysis based upon the input impedance concept. 2) Characterize the time course of development of atherosclerotic lesion in a perivascular fibrosis (Saran Wrap^{R} induced) versus sham-operated pig carotid artery model. 3) Correlate the analysis of the pulsatile pressure/flow relationship with observed histomorphological changes. Two tubes with different static compliance were tested in a mock circulatory loop and *in vivo* in 6 dogs. The *in vitro* results showed the stiffer of the 2 tubes had higher values for Zmax, Fzmax and the reflection coefficient. The same trends were seen *in vivo*. Marked histomorphological changes were seen in carotid arteries from a high cholesterol diet fed group of pigs versus a normal diet fed group. The normal diet pigs had essentially normal arteries, irrespective of wrapping. Wrapped common carotid arteries, inthe atherosclerotic diet fed group, showed more advanced lesions than their contralateral, sham operated, arteries. The input impedance derived parameters did not correlate with the histomorphological changes seen. We expected the wrapped vessels with marked atherosclerotic lesions to be stiffer, therefore the input impedance derived parameters should have been higher. Inconsistent changes were found in 3 of the 4 pigs with advanced lesions.

(Supported, in part, by funding from the Texas Engineering Experiment Station).

17.6

ACTIVE CUTANEOUS VASODILATION DESPITE DEFICIENCY IN VASOACTIVE INTESTINAL POLYPEPTIDE IN HYPERTHERMIC MEN WITH CYSTIC FIBROSIS. M.V. Savage*, G.L. Brengelmann, A.M.J. Buchan*, and P.R. Freund*. Simon Fraser University, University of Washington, Seattle, WA, 98195, and University of British Columbia.

The transmitter substance that brings about the active cutaneous vasodilation that accompanies sweating during hyperthermia is unknown. Hökfelt, *et al.*, (*Nature*, 284:515-21, 1980), hypothesized that it is vasoactive intestinal peptide (VIP), co-transmitted with acetylcholine during activation of sweat glands. An experimental model for testing this hypothesis was suggested to us by the report from Heinz-Erien, *et al.* (*Science*, 229:1407-8, 1985), that VIP innervation is sparse in the skin of persons with cystic fibrosis (CF). In hyperthermic men with CF (4 subjects), forearm blood flow (by venous occlusion plethysmography) was within the range spanned by hyperthermic controls (4 subjects) and coincided with near-normal increase in sweating.

Immunocytochemical analysis of skin biopsies confirmed the sparsity of VIP innervation in the CF subjects; also neuropeptide Y fibers were sparse. Merkel cells differed in position and orientation. Substance P and calcitonin gene-related peptide-immunoreactive fiber densities were similar in CF and control subjects. Since VIP was not totally absent in the skin of CF subjects, our findings do not rule it out as the transmitter for active cutaneous vasodilation. Nonetheless, they make other vasodilator peptides appear more likely candidates. Supported by NIH HL-16910.

NEONATAL CIRCULATION

18.1

EFFECT OF THEOPHYLLINE ON REGIONAL DISTRUBUTION OF BLOOD FLOW DURING HYPOXIA. A Cote* M. Amies* H Porras* (SPON: A L Coates) McGill Univ. Montreal, Canada.

Since 1) hypoxia influences regional distribution of blood flow in newborns and 2) theophylline (THEO), an adenosine inhibitor, influences cardiovascular function, we studied regional distribution of blood flow and O_2 delivery in normoxia and after 30 minutes of hypoxia (PaO_2= 42 torr) during a control period (CONTROL) and after a parenteral infusion of THEO which achieved a blood level of 40 umol/L. Five piglets (age: 6-7 days) were studied in the quiet state, 2 days after they had been instrumented for blood flow measurement (microspheres). Mean arterial O_2 content fell from 11.4 ml% to 7.6 ml% during hypoxia. In the CONTROL, blood flow and O_2 delivery to the heart and diaphragm increased with hypoxia; other organs (such as brain, adrenals, small intestine and skeletal muscles) had an increase in blood flow just to maintain O_2 delivery; finally O_2 delivery dropped to some organs (kidneys, colon and skin) with hypoxia. This pattern of regional distribution of blood flow and O_2 delivery with hypoxia was unchanged after THEO.
In conclusion, theophylline, at doses used therapeutically in newborns, has no significant effect on the circulatory adjustment to moderate hypoxia in piglets. If adenosine is implicated in the redistribution of blood flow observed with hypoxia, the dose of theophylline used in our studies is not sufficient to inhibit adenosine.

18.2

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) INDUCED CARDIAC DYSFUNCTION IN NEWBORN LAMBS. Lee A. Pyles*, Elizabeth A. Stejskal*, Randal P. Marchessault*, Thomas P. Green* and Stanley Einzig, University of Minnesota, Mpls MN 55455

ECMO is used to treat severe cardiac and pulmonary dysfunction in children. However, cardiac dysfunction often occurs following ECMO. We hypothesized that a form of myocardial stunning, mediated by oxygen radicals and lipid peroxidation (LPO), is produced and could be modeled in lambs. In 6 anesthetised newborn lambs, catheters were placed in the pulmonary artery (PA), right atrium (RA), coronary sinus (CS), aorta (AO) and left ventricle (LV). Biomedicus® vortex pump flow was set at 100 ml/kg/min. LPO was assessed by the reaction of thiobarbituric acid with malondialdehyde (MDA). LV shortening fraction (SF) was measured by cardiac echo. SF, pressures and PA, CS and AO hematocrits, blood gases and MDA levels were measured at control (C) and 0.5, 1, 2 and 4 hours of ECMO. SF decreased from 34 ±6% (SD) at C to 11±3% at 0.5 h. ($p < 0.001$) and tended to be lower than C for the remainder of the experiment (2h: 20±12%). C and 0.5 h ECMO values for other parameters are as follows: LV end diastolic dimension 14.5±1.5 vs. 15±5mm; AO pressure 79 ±14 vs. 54 ±12 mm Hg ($p < 0.005$); PA wedge pressure 11±3 vs. 14 ±3 mm Hg; heart rate 206 ±34 vs. 187 ±20 beats/min; AO pH 7.41 ±0.03 vs. 7.29 ±0.09 ($p < 0.05$); AO PO2 70 ±8 vs. 432 ±60 torr ($p< 0.001$). CS and PA PO2 were also significantly increased. AO and CS MDA levels tended to increase: AO,1.04±0.43 vs. 1.70±0.74 nmole/ml (p=0.08); CS, 0.94±0.28 vs. 1.86±0.84 nmol/ml (P=0.06). ECMO induced cardiac dysfunction in newborn lambs may be associated with oxidative damage but will require further study. Deleterious changes in cardiac preload, afterload and heart rate do not appear to be involved.

18.3

ONTOGENY OF OVINE PULMONARY VASCULAR RESPONSES TO ENDOTHELIUM-DEPENDENT AND -INDEPENDENT DILATORS IN VITRO. SH Abman, BA Chatfield*, DM Rodman, SL Hall*, and IF McMurtry. Departments of Pediatrics and Medicine, University of Colorado School of Medicine, Denver, CO 80262

To examine vasoreactivity of the perinatal pulmonary circulation, we studied the effects of endothelium-dependent (acetylcholine, ACH; adenosine diphosphate, ADP) and -independent (sodium nitroprusside, SNP) dilators on tone of isolated small pulmonary artery rings harvested from freshly-sacrificed late-gestation fetal, neonatal (1-4 wks), and adult sheep. Changes in isometric force of rings precontracted with phenylephrine in baths aerated with 21% O2/5% CO2 gas mixtures were measured after the addition of incremental amounts of ACH, ADP or SNP.

	ACH		ADP		SNP	
	MAX REL	EC50	MAX REL	EC50	MAX REL	EC50
FETUS	17±3*	15 x 10-6*	14±5*	2 x 10-6	100	5 x 10-8
NEWBORN	51±5	5 x 10-6	43±6	3 x 10-6	100	2 x 10-8
EWE	70±8	2 x 10-6	44±2	1 x 10-6	100	1 x 10-8

(MAX REL = maximal relaxation; * = $p<0.05$, vs. newborn, ewe)

We conclude that conducting fetal pulmonary vessels have little response in vitro to endothelium-dependent dilators, but have similar relaxation to an endothelium-independent dilator, SNP, when compared with newborn and adult rings. We speculate that maturational changes in endothelial function may contribute to ontogenetic differences in pulmonary vasoreactivity.

18.4

HEMODYNAMIC EFFECTS OF HEAT-KILLED GROUP B STREPTOCOCCUS IN NEWBORN LAMBS: CONTRIBUTION OF PEPTIDO-LEUKOTRIENES. Michael D. Schreiber, Lorna J. Torgerson* and Robert F. Covert*.
Michael Reese Hospital and University of Chicago Pritzker School of Medicine, Chicago, IL 60616

Group B beta-hemolytic Streptococcus (GBS) is an important cause of neonatal sepsis and persistent pulmonary hypertension. The acute pulmonary hypertension is felt to be mediated by thromboxane. In this study, we characterized the dose-dependent response of chronically instrumented spontaneously breathing newborn lambs to multiple injections of heat-killed GBS (0.1 to 9ml 10^{-9} GBS) and attempted to block the response with the putative leukotriene receptor antagonist WY48,252 (1,1,1-trifluoro-N-3-(2-quinolinylmethoxy)phenyl]methanesulfonamide)(30mg/kg IV). In 6 lambs, GBS caused a dose-dependent ($p<0.001$) increase in pulmonary ($y=13.9x + 21$, $R=0.70$) and systemic ($y=11.1x + 11.8$, $R=0.62$) arterial pressures and decrease in cardiac output ($y=-46.2x - 43.3$, $R=0.62$). Arterial oxygen tension was not significantly affected. WY48,252 caused a 25% decrease in GBS-induced pulmonary hypertension ($n=3$, $p< 0.09$) but did not affect the systemic response. Thus, leukotrienes in addition to thromboxane may contribute to GBS-induced pulmonary hypertension. Supported by an American Lung Association grant. WY48,252 was a kind gift from Dr. Chang, Wyeth-Ayerst Research, Princeton, NJ.

19.1

ENDOGENOUS HEAT PRODUCTION IN TWO GRASS DWELLING CICADAS FROM SOUTH AMERICA (HOMOPTERA: CICADIDAE). Allen F. Sanborn*, James E. Heath, Fernando G. Noriega*†, and Maxine S. Heath*. University of Illinois, Urbana, Il. 61801 and †University of Arizona, Tucson, AZ 85721.

Proarna bergi (Distant) and Proarna insignis Distant used metabolic heat to raise body temperature for activity when ambient conditions would prevent activity in ectothermic animals. Both species could sing during overcast or rainy conditions. Body temperatures in the field exceeded ambient by as much as 7.4C when solar radiation was unavailable to the insects. In the laboratory voluntary metabolic heat production raised body temperature as much as 12.3C and 10.7C above ambient temperature in P. bergi and P. insignis respectively. Estimates of metabolic rate from heating and cooling curves were 0.65 $ml O_2$/min for P. bergi and 0.61 $ml O_2$/min for P. insignis. Fine shiver-like movements of the thoracic musculature produced the heat. Endogenous heat production uncoupled reproductive behavior from environmental constraints.

Supported by USPHS Traineeship GMS07143 (AFS), Sigma Xi (AFS), Tinker Foundation (AFS & MSH), Fulbright (JEH), and S.P.I.D.E.R. Argentina (FGN).

19.2

HEAT EXCHANGE BY THE PINNA OF THE AFRICAN ELEPHANT (Loxodonta africana). Polly K. Phillips* and James E. Heath. University of Illinois, Urbana, IL 61801

Surface temperatures of the pinna of four female African elephants were measured at ambient temperatures of 23, 27, and 32 C using infrared thermography. Instantaneous heat losses calculated using those values ranged from 4.3 to 76.2 Watts, under the observed conditions. Using a value of 17 Kcal/kg/day, those heat losses account for .26 to 4.64% of the animals' standard metabolic rates, considering one side of one ear only. A model of heat flow across a flat vertical plate was constructed and compared to the actual values. Up to 100% of an African elephant's heat loss needs can be met by movement of its ears and by vasodilitation. Thermography indicates the heat distribution pattern across the pinna changes with ambient temperature and that areas of specialized vasomotor control exist.

The animals used in this study were made available through the courtesy and generosity of the Brookfield Zoo, Brookfield, Illinois.

19.3

KIDNEYS OF THE RHINOCEROTIDAE. N.S.R. Maluf. Cleveland, Ohio. 44107.

Kidneys of the following were studied anatomically: Rhinoceros unicornis, Diceros bicornis, and Ceratotherium simum. Features in common occur in no other mammal and are of greatest interest. The ureter branches into a cephalic and a caudal intra-renal fibro-muscular conduit into which open 18 to 25 orifices of the primary infundibula which are the urinary outlets of the 57 to 78 tightly apposed renal lobes. Some of the infundibula branch so that every lobe has an infundibulum. An enlarged collecting duct (tubus maximus) receives the terminal collecting ducts of its lobe. In neonate and adult the glomerular capsules do not vary in size across the cortex. The interlobar arteries pass through and branch within the interlobar septa and send out numerous branches which perforate the septa and thus enter the cortices of adjacent lobes. In their course to the cortico-medullary border, where they become arcuate arteries, they send out intralobar branches. At the cortico-medullary border arcuate veins anastomose with one another and enter the large intralobar veins at the infundibula. The interlobar veins enter a large central vein which courses directly medial to the conduits. The cortex of D. bicornis is 65% of renal mass; number of glomeruli in both kidneys is about 25 million.

COMPARATIVE PHYSIOLOGY: CIRCULATION AND RESPIRATION

20.1

EXTRACTION AND METABOLISM OF SEROTONIN BY THE PERFUSED TROUT GILL. D.E. Kullman* and K.R. Olson, Indiana Univ. School of Medicine, South Bend Center, Univ. of Notre Dame, Notre Dame, IN 46556.

The perfused trout gill inactivates circulating catecholamines by extraction and metabolism (Am. J. Physiol. 250:R526, 1986). The present study examined serotonin (5-HT) inactivation by the perfused gill of Salmo gairdneri. ^{3}H-5-HT and ^{14}C-sucrose (volume marker) were continuously or bolus perfused through the gill and effluent from the arterioarterial (AA; respiratory) and arteriovenous (AV; central sinus) pathways, counted for radioactivity and analyzed by HPLC-EC. After 5, 30, 60, 120 and 180 min of continuous perfusion ^{3}H recovery from the AA pathway was 55±4, 78±4, 84±4, 87±2 and 90±3%, respectively (N=5); AV recovery during the same period was 45±2, 79±4, 92±5, 103±4, 106±6%. HPLC of the effluent indicated that less than 20% of ^{3}H recovered was 5-HT. Three metabolite peaks were observed, one coeluted with the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA); other peaks have not been identified. ^{3}H recovery by gills perfused with a ^{3}H-5-HT bolus was 62±6%. (AA pathway; N=5) Imipramine (I; 10^{-5}M) or I plus cocaine (C; 10^{-5}M) increased ^{3}H recovery by 11±4% or 18±4%, respectively. 5-HT was the predominant ^{3}H-labeled amine in gills pretreated with I or I+C. These results indicate that trout gills extract and metabolize 5-HT and that the uptake process is sensitive to I and C inhibition.

Supported by NSF Grant No. DCB 8616028.

20.2

EARLY VENTILATORY EFFECTS OF ROTENONE IN THE TOXIC REACTION OF TWO MARINE TELEOSTS: *Haemulon flavolineatum* & *Holocentrus rufus*. C. J. Wingard*, and D. J. Hautau* (SPON: C. J. Swanson)

Routine use of Rotenone (& other rotenoids) as a piscicide for removal of undesirable freshwater fish populations is well documented. However, few studies have been directed at its toxicity on marine fauna. Accordingly, adult *H. flavolineatum* & *H. rufus* collected locally in Ferry Reach, Bermuda, were held in filtered, running seawater tanks prior to experimental use. From a stock solution of rotenone (extracted from Cube root,46.6%) in 95% ETOH, a series of both species were exposed chronically to 5,25,50, & 75 µg/L doses; ETOH alone and seawater exposure serving as controls. Early ventilatory changes were monitored by opercular impedance electrodes routed from an A/D recording system; all data were saved to disc for post processing. Ventilation rate and amplitude decreased significantly in a time/dose dependent manner for both species as against controls. Depending upon dose, an initial, transient compensatory increase in ventilation rate was followed by a similar, linear reduction in rate for both species until total asphyxiation was manifest. However, the time course of change in gill amplitude was distinctly different between the two species, particularly at dosages ≥ 50 µg/L. Systemic reduction in gill perfusion has been proposed as a major toxic mechanism, however cytotoxic effects on chloride cells and osmoregulation due to blocking of respiration are noted contributing factors. Under the conditions employed, all doses proved fatally toxic.

20.3

HEART RATE AND VENTILATION/APNEA DURING THE FEEDING MANEUVER IN THE COMMON ANOLE, (*Anolis carolinensis*). C. J. Swanson, D.J. Hautau*, and Christopher Wingard*. Wayne State University, Detroit, Michigan 48202

Few studies have attempted to quantify the feeding maneuver (s) and associated changes in heart rate and ventilation in lizards. Adult *Anolis carolinensis* were instrumented transthoracically with pneumographic impedance electrodes plus an extracorporal transducer sensing tail-base pulse pressure. After obtaining baseline recording of resting heart rate and ventilation rate and relative, volume in a standardized conditioning chamber, individual *A. carolinensis* were presented a prey selection coincident with the triggering of a 2-channel A/D system (Computerscope) and simultaneous video overlay recorded to a VCR. Physiological data were saved to disc, and together with freeze-frame video playback and digitization, post-acquisition analysis allowed for coincident measurements of the motor maneuver (ie.point of attack, instantaneous velocity, deglutition) plus transient changes in heart and ventilatory rate prior to, during, and several minutes after prey capture. Consistent findings across all animals examined (n= 12) were: significant elevation in heart rate ($\bar{x}$ = 79 rBPM), lasting several minutes and a characteristic, variable period of apnea during prey seizure through deglutition. The duration and frequency of apneal episodes correlated primarily to prey size and appears to be a common and consistent feature in the feeding maneuver of the common anole, *A. carolinensis*.

MICROCIRCULATION

21.1

A LOW COST SYSTEM FOR MONITORING ARTERIOLE DIAMETER BY ON-LINE COMPUTER ANALYSIS OF TELEVISION IMAGES. T. O. Neild* (SPON: J.H. Szurszewski). Department of Physiology, Monash University, Clayton, Victoria 3168 Australia

In isolated preparations of arterioles the edges of the arteriole are usually visible as dark or light lines, depending on the nature of the connective tissue in which they are embedded. Arterioles in the pia or the submucous plexus of the intestine usually have dark edges, whereas arterioles in subcutaneous connective tissue have light edges. A system for tracking the diameter of arterioles with dark edges has been developed (Neild, 1988; Blood Vessels 26:48-52). The darkest horizontal line in a restricted region is found by summing the pixel brightness values along lines and finding the minimum of the sum. Two regions enclosing opposite edges of the arteriole are examined, and the difference in edge position is sent to a D-A converter to give a trace of diameter on a chart recorder. The present system uses a modified version of this technique to allow the choice of tracking either dark or light edges, and to use the Arlunya FG304 combined frame grabber/D-A converter card. This results in a considerable reduction in the cost of the equipment while still permitting around 5 measurements/second of arteriole diameter.

21.2

ANALYSIS OF CAPILLARY GEOMETRY IN EPICARDIUM AND ENDOCARDIUM OF RAT HEART. David C. Poole and Odile Mathieu-Costello. Dept. of Med. M-023A, Univ. of California, San Diego, CA 92093.

The high energetic requirements of cardiac muscle present an extreme challenge to gas exchange. A major determinant of tissue gas exchange potential is **capillary surface area per volume of muscle fiber, $S_V(c,f)$,** estimation of which necessitates quantification of capillary orientation. Because regional differences in capillary supply of myocardium have been reported, we applied morphometric techniques to analyze capillary geometry systematically in epi- (EPI) and endo-cardium (ENDO) of glutaraldehyde perfusion fixed rat heart (n=4). On 1-μm sections cut rigorously transverse and longitudinal to the muscle fiber axis we determined: capillary/ mm^2 on transverse, $Q_A(0)$, and longitudinal, $Q_A(\pi/2)$, sections, capillary diameter, d(c), fiber cross-sectional area and sarcomere length, l. $S_V(c,f)$ was computed as $\pi * d(c) * J_V(c,f)$ where **$J_V(c,f)$ is capillary length per fiber volume** determined on the basis of a directional distribution model of capillary segments (Fisher axial; validated previously in skeletal muscle; Mathieu et al. J. Microsc. 131: 131-146, 1983). Analysis of capillary density, $Q_A(\alpha)$, in sections taken at angles α (from 0 to $\pi/2$ to fiber axis) provided a good fit to capillary segment orientation in cardiac muscle. No systematic difference was found in fiber size, capillary diameter (EPI=4.9±0.3; ENDO=4.5±0.2 μm), $J_V(c,f)$ (EPI =6302±558; ENDO=5957±492 mm^{-2}) or $S_V(c,f)$ (EPI=968.1±76.5; ENDO= 838.2±93.0 cm^{-1}) between EPI and ENDO. Contribution of capillary tortuosity and branching to $J_V(c,f)$ ranged from 6-27% (EPI) and 8-21% (ENDO) over the ranges of l considered (EPI= 2.09-2.23; ENDO=2.04-2.17 μm). We conclude that there is no systematic difference between EPI and ENDO with respect to capillary surface density when fiber and capillary orientation are accounted for. These data are consistent with homogeneous distributions of mitochondrial volume density and maximal blood flows in epi- and endocardium. Supported by NIH (07212 and 17731) and Am. Lung Assoc. of CA.

21.3

COMPUTERIZED IMAGE ANALYSIS OF ADIPOSE TISSUE PHOTOMACROGRAPHS: EVIDENCE OF NEOVASCULARIZATION WITH OBESITY. David L. Crandall, Gregory D. Ferraro* and Peter Cervoni*. Dept. Cardiovasc. Res., American Cyanamid Co., Medical Res. Div., Lederle Labs., Pearl River, NY 10965

We have repeatedly observed different patterns of vascularity in adipose tissue from rats during various stages of the development of spontaneous obesity. To quantitate vascularity, representative skin flaps overlying the subcutaneous adipose tissue of either an obese, formerly obese, or lean rat were photographed at 1 x magnification with a Nikon Multiphot apparatus. These photomacrographs were subsequently analyzed with a Quantimet 970 image analysis system, and "area fractions" indicated the relative amount of surface area occupied by the vessels. Vascularity was similar between obese and formerly obese, weight reduced animals, both of which were greater than the lean value. Additional characterization of the pattern of vascularity with obesity included interdepot quantitation of vascular protein from anatomically distinct sites of fat deposition. These data clearly indicated a greater vascular protein concentration per gram of mesenteric adipose tissue, when compared to epididymal and retroperitoneal content. These studies imply an active neovascularization during the expansion of adipose tissue in obesity which is maintained even after weight reduction, and further suggest that the potential for increased vascular capacity may be dependent upon the site of lipid deposition.

21.4

3-D MODEL OF VASCULAR NETWORK OBTAINED BY STEREO VISION TECHNIQUES. Shanti J. Aggarwal, Nak H. Kim, Kenneth R. Diller and Alan C. Bovik (Spon: J. L. Larimer) University of Texas, Austin, Texas 78712

The quantitative analysis of the depth of injury, penetration of therapeutic agents in tissues and regeneration of vascular patency after graded degree of thermal injury requires a knowledge of the shape and spatial configuration of the vascular networks in the tissue. We have applied computational stereo-microscopic vision techniques to describe the three-dimensional configuration of microvessels in full thickness rat skin vascular casts produced by perfusion of Yellow Microfil latex solution through the aorta.

The algorithm is based on integration of the output of a stereo matching procedure (disparity information) with the 2-D representation of the monocular visual processing of one of the stereo images and the 3-D shape description of vessels is expressed in terms of a set of space curves. The planar curve representation is computed by: (1) applying an edge detector to delineate the vessel boundaries, (ii) filling-in of the vessel interior so that a binary image of the network as a separate region is obtained, (iii) deriving an eight-connected chain representation of the vessel using a skeletonizing process, and (iv) parametering the resulting planar curves. The intensity gradient based disparity information of different segments in the curve in the stereo pair images is then computed. The set of planar curves obtained after monocular processing are finally integrated with intensity gradient based disparity information to yield a dense depth map and a topological representation of the microvessels in the rat skin are computed by interpolation and triangulation. The connectivities of different segments is examined on the basis of (i) continuity in slope and (ii) continuity in depth. The 3-D space curves so obtained can be converted to generalized cylinder representation for the graphical display of the vessel network. Data obtained after processing of the vascular casts will be presented.

The grant support from the National Science Foundation(ECS 8513123), the Whitaker Foundation and the the Texas Advanced Technology Program is gratefully acknowledged.

21.5

VASCULAR SMOOTH MUSCLE ACTIVATION STATE INCREASES WITH MYOGENIC TONE IN ISOLATED ARTERIOLES.

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Implicit in the definition of the myogenic response is the concept that arterial smooth muscle (VSM) shifts to a different length-tension curve when lumenal pressure is altered. Direct evidence support to this idea is lacking, however, because VSM mechanics are generally studied in large vessels without myogenic tone. To test the hypothesis that the arteriolar myogenic response represents a shift in both VSM activation state and length, single arterioles (15-35 μm, i.d.) were dissected from hamster cheek pouch, cannulated with micropipettes, and studied in vitro. Diameters were recorded on videotape at high magnification while lumenal pressures were controlled using a pressure reservoir-pump system. A modified isotonic release protocol was used to estimate the velocity of shortening at various "holding" pressures (i.e. preloads) within the myogenic range of an arteriole. Rapid arteriolar diameter changes were measured via frame-by-frame playback over the time period immediately following quick "release" from a given holding pressure to a series of lower pressures (i.e. afterloads). The data for each release trial were fit by a single exponential whose exponent was then plotted as a function of afterload. Velocity of shortening at zero load ($V_{max'}$) was determined by fitting the data for each preload to the Hill equation. $V_{max'}$ increased with preload over the myogenic range of an arteriole. Since $V_{max'}$ is an indicator of muscle activation state, we conclude that a myogenic constriction represents a shift in both length and activation state of arteriolar smooth muscle. Supported by NIH HL-38104 and AHA 881121.

21.6

RESPONSE OF LARGE AND SMALL ARTERIOLES IN RAT CREMASTER MUSCLE TO CONTINUOUS- AND BURST-FREQUENCY SYMPATHETIC STIMULATION.

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The diameter and flow responses of 1A and 3A arterioles in rat cremaster muscle to continuous- and burst-frequency stimulation of the lumbar sympathetic chain (L1-L2) was measured by intravital microscopy. Continuous-frequency stimuli (CFS) of 1, 2, 4 and 8 Hz were applied for 1 min. Burst-frequency stimuli (BFS) of 1 sec duration and intraburst frequency of 30 Hz were applied at interburst intervals of 30, 15, 7.5 and 3.75 sec for a 1 min period. The interburst intervals were chosen so that the total number of stimuli delivered by BFS during the 1 min period was equivalent to one of the CFS patterns. In the 3A, the BFS produced greater maximal vasoconstriction and flow reduction than CFS. When the diameter and flow responses to CFS and BFS were time-averaged over the 1 min stimulus period and compared to control values, the responses were not different at any equivalent level of stimulation in either the 1A or 3A. Irreversible, nonselective α-blockade by suffusion of 10^{-5}M benextramine for two 15 min periods eliminated the vasoconstrictor response to topical application of 10^{-4}M norepinephrine, however, a vasoconstrictor response to BFS was retained in the 3A and to CFS and BFS in the 1A. Both large and small arterioles in rat skeletal muscle respond effectively to sympathetic stimulation applied in high frequency bursts which simulates the normal pattern of nerve discharge. A portion of the response appears to be nonadrenergically mediated. (Support NHLBI 36552)

21.7

SYMPATHETIC NERVE STIMULATION (SNS) ACTIVATES POSTJUNCTIONAL α1- BUT NOT α2-ADRENOCEPTORS (AR) ON LARGE ARTERIOLES.

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The relative roles of postjunctional α1- and α2-AR during SNS remain unclear. In the present study arterioles (120 μm diam.), which we showed previously possess both AR types, were examined in rat cremaster skeletal muscle during efferent SNS (decentralized lumbar sympathetic chain, 1-16Hz, 7V, 3 msec, 2 min). The cremaster was suspended in a tissue bath containing propranolol and diameter was measured with intravital microscopy. Frequency-response curves were obtained after addition to the bath of vehicle, prazosin (PRZ) or rauwolscine (RWL). Diameters in percent of baseline were (*p <0.05 vs Vehicle):

		SNS Stimulation (Hz)					
Group	no. animals	1	2	4	8	12	16
Vehicle	8	88±3	84±5	77±5	73±3	61±3	61±2
RWL, 1E-7M	5	86±6	75±6	69±7	63±6	58±3	59±3
RWL, 5E-7M	3	89±2	73±3	63±3	59±2	61±8	67±5
PRZ, 1E-7M	7	92±2	90±2	88±3	88±3*	79±5*	77±3*
PRZ, 5E-7M	6	92±1	94±3	91±4	94±7*	92±5*	89±5*

Constriction was strongly and dose-dependently inhibited by PRZ, while RWL instead tended to enhance constriction, presumably due to presynaptic α2 AR inhibition. Thus, only α1 ARs appear to be "innervated" on large arterioles. However based on other studies, SNS of small terminal arterioles which are also innervated and have primarily α2 AR, may rely predominantly on α2 AR. (support: NIH-NHLBI, 38783)

21.8

INTERACTIONS BETWEEN α1- AND α2-ADRENOCEPTORS (AR) AND A2 PURINOCEPTORS ON MICROVASCULAR SMOOTH MUSCLE.

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We previously found that arterioles and venules in skeletal muscle microcirculation possess both postjuctional α1- and α2-AR, and that α2 (but not α1) constriction is inhibited by tissue acidosis or ischemia. Here we examined with intravital microscopy if AD selectively antagonizes α-AR constriction of arterioles and venules. The acutely denervated rat cremaster was suspended in a tissue bath. Concentration-response (diameter) curves were obtained for norepinephrine (NE) in the presence of 1E-6M rauwolscine (RWL) or 1E-7M prazosin (PRZ) to examine the effect of the AD agonist 5-(N-ethyl)carboxyamido-adenosine (NECA, 2E-8M, EC50 against NE) on α1- and α2-AR, respectively; *p< 0.05, ** p< 0.01 vs vehicle (NL regression).

		NE+RWL:		NE+PRZ:	
	n	Arteriole -Log EC50	Venule -Log EC50	Arteriole -Log EC50	Venule -Log EC50
Vehicle	6	6.8±.09	6.1±.07	6.6±.10	6.2±.06
NECA	6	6.0±.07**	5.3±.06**	6.3±.04*	5.9±.06**

EC25 analysis revealed an even greater difference in α1-AR versus α2-AR sensitivity to AD receptor stimulation. AD (2.2E-6M, EC50 against NE) had effects similar to NECA that were reversed by the AD antagonist, xanthine amine congener (7E-7M). These data indicate that, unlike tissue acidosis or tissue hypoxia, both α1- and α2-AR constriction are inhibited by adenosine A2-type receptor stimulation, with α1-AR exhibiting a 3- to 4-fold greater sensitivity than α2-AR.

21.9

MAXIMAL VASODILATION OF RAT CREMASTER MUSCLE ARTERIOLES FOLLOWING ß-ADRENERGIC STIMULATION.

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Adrenergic receptors of the $ß_2$ subtype mediate vasodilation in several vascular beds but were found to dilate arterioles in rat cremaster arterioles only 10-20% above their control diameters (Koo, *J. Cardiovasc. Pharm.* 1984, 6(5):897), a small response considering the large depressor effect of systemically delivered ß agonists. To further explore the vasodilator capacity of the $ß_2$ receptor pathway in skeletal muscle microvessels we used an *intra vital* microvascular preparation in which the acutely denervated cremaster muscle of the urethane-chloralose anesthetized rat was suspended in a tissue bath filled with recirculating modified Krebs solution containing catecholamine reuptake blockers cocaine and normetanepherine, and the α-antagonist phentolamine. Systemic blood pressure and core temperature were measured and temperature, pO_2 and pH of the bathing solution were monitored and automatically adjusted. In each experiment one to four arterioles (25 μm mean dia.) were viewed through the videomicroscope and recorded on tape. Following a baseline period isoproterenol (ISO) or the $ß_2$ selective agonist albuterol (ALB) were incrementally added to the bathing solution in the absence or presence of the $ß_2$ selective antagonist butoxamine. At the end of the experiment nitroprusside (NP) was added to reveal the full dilator potential of the vessels. ALB acted as a partial agonist, producing half maximal vasodilation relative to NP. ISO produced equal vasodilation to NP at a maximal concentration of 10^{-7}M with an A_{50} of $3X10^{-8}$M. Butoxamine abolished the response to either agonist confirming their action through the $ß_2$ receptor pathway. Denervation of the muscle, and reuptake and α-adrenergic blockade may have allowed the full $ß_2$ response (>200% dilation over control) in this study as compared to other studies where much lower maximal responses were found.

21.10

PRECONSTRICTION UNMASKS SEROTONIN-INDUCED DILATION OF LARGE ARTERIOLES IN SKELETAL MUSCLE.

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Serotonin (5-HT) constricts large arterioles (A1) in skeletal muscle, but dilates small arterioles. In anesthetized rats, A1s have little resting tone so any dilator potential of 5-HT could be masked. A1s were preconstricted to increase tone. The cremaster muscle (with intact nerve and blood supplies) was suspended over an optical port in an environmentally controlled tissue bath. A1s were observed via closed-circuit television microscopy during sequential doses of 5-HT to the bath. A cyclo-oxygenase inhibitor was present to prevent prostaglandin-induced dilation. Angiotensin II (AII, 10-7M), added to the cremaster bath, gave a 30±3% reduction in diameter in the preconstricted group (PC). Data are presented as percent change from baseline diameter (BL) for the control (C) group and as percent change from the diameter after AII preconstriction for the PC group. (* p<0.05, C vs PC)

	BL	AII	Response to 5-HT (M)				
	μm	μm	10-8	10-7	10-6	10-5	10-4
C	83±4	---	+10±13*	+3±6*	-10±6*	-31±5*	-33±5*
PC	95±6	65±2	+23±5	+38±8	+36±8	+15±6	+22±7

Preconstricted A1 arterioles dilated but non-preconstricted A1 arterioles constricted in response to topical 5-HT application. These data indicate that two 5-HT receptors are present on large A1 arterioles: one mediating constriction and another mediating dilation.

21.11

NEUROKININ A IS A POTENT VASODILATOR PEPTIDE IN THE CANINE FORELIMB PERFUSED AT NATURAL FLOW. David E. Dobbins, Molly J Buehn,* and Joe M. Dabney. Department of Physiology, USUHS, Bethesda, MD 20814-4799.

Neurokinin A is a 10 amino acid peptide of the tachykinin family which can be found in high concentration in the perivascular nerves innervating the resistance vessels of the peripheral circulation. In the current study we have infused neurokinin A at three infusion rates (.01, .1, and 1 μg/min. for thirty minutes at each infusion rate) in the isolated, innervated canine forelimb perfused at natural flow (n=9). We measured large artery and vein pressures, small artery and vein pressures and blood flows in both the skin and skeletal muscle circulations for the calculation of total and segmental vascular resistances. Infusion of the lowest dosage of neurokinin A resulted in transient decreases in total forelimb and total muscle resistances. The middle dosage resulted in a 25% decrease in total forelimb resistance which was equally distributed between the skin and skeletal muscle circulations. The highest dosage of neurokinin A resulted in a 57% decrease in total forelimb resistance which was again equally distributed between the skin and skeletal muscle circulations. The sustained decreases in forelimb resistances produced by the two highest dosages of neurokinin A were manifest in both large artery and small vessel resistances. The potent effects of neurokinin A on vascular resistance and its concentration in perivascular nerves innervating the resistance vessels of the circulation suggests a potential role for neurokinin A in control of the circulation in either physiological or pathophysiological states.

21.12

Capillary Endothelial Adenosine Transport in Isolated, Perfused Rat and Guinea Pig Hearts. D.E. Mohrman, R.A. Nelson*, J.E. Sherin*, and L.J. Heller. University of Minnesota, Duluth, MN 55812.

We used a mathematical model of transcapillary adenosine movement to estimate the permeability x surface of capillary endothelial cell membranes to adenosine (PS_{ecl}) and the capacity of endothelial cells to metabolize adenosine (G_{ec}) in isolated, perfused rat and guinea pig hearts. The model was used to find best fits to sets of arterial, venous (C_v) and interstitial (C_{isf}) adenosine levels recorded during steady-state perfusion with 0,0.1, 0.3 and 1.0 μM adenosine. Adenosine concentrations were determined with HPLC techniques. C_{isf} was taken to equal that measured in samples of epicardial exudate fluid. Average results (mean ± SE) of the modelling analysis were as follows:

	n	PS_{ecl} ($ml \cdot g^{-1} \cdot min^{-1}$)	G_{ec} ($ml \cdot g^{-1} \cdot min^{-1}$)
Guinea Pig	6	12±1	37±9
Rat	7	84±28*	706±259*

We conclude that the capillary endothelial cells of the isolated rat heart have significantly larger PS_{ecl} and G_{ec} than those of the isolated guinea pig heart (*=$p<0.05$). Our analysis indicates that under control conditions at a perfusion rate of 10 $ml \cdot g^{-1} \cdot min^{-1}$, C_{isf} would be 5±1 times C_v in isolated guinea pig hearts and 11±4 times Cv in isolated rat hearts. (Supported by USPHS NIH Grant HL 35869).

21.13

UNIQUE PERMEABILITY-SURFACE AREA (PS) PRODUCTS AND REFLECTION COEFFICIENTS (σ) IN THE FELINE SMALL INTESTINE. M.I. Townsley, R.K. Reed, and A.E. Taylor. Department of Physiology, University of South Alabama, Mobile, AL 36688.

We have used a new analysis of lymphatic flux data (Reed et al. FASEB J. 3:A1399, 1989) based on a unique property of the Peclet number (x) to determine PS-products and σ for total proteins in the small intestinal microvasculature. Steady state lymph flows (Jv), and plasma (Cp) and lymph (Cl) total protein concentrations were obtained from the autoperfused cat ileum (n=7, 43.6±2.0g, mean±SE) at venous outflow pressures ranging from 0 to 30 mmHg. The relationship between lymph protein flux (JvCl) and Jv is dominated by diffusion (93±2% of total flux in this study) through small pores at low Jv. After the transition (at the maximal diffusion point, Max,diff) from a curvilinear to a linear relationship, the slope is defined as $(1-\sigma)Cp$. σ assigns a unique value to x at Max,diff, and then $PS = (1-\sigma) \cdot Jv_{Max,diff} / x_{Max,diff}$. Jv and x at Max,diff averaged 91.3±18.9 μl/min/100g and 0.26±0.03, respectively, yielding a PS of 14.7±4.3 μl/min/100g. σ was 0.95±0.01, a value higher than that calculated using the lymph washdown technique in the same preparation (0.88±0.01, $p<0.05$). This difference is likely due to the finding that the majority of the protein flux was still diffusive (63±8%) at the highest lymph flows attainable in these studies (an average of 26 fold greater than baseline). Supported by HL39045 and HL22549.

21.14

INCREASED NEGATIVITY OF INTERSTITIAL FLUID PRESSURE (IFP) IN INFLAMMATORY EDEMA IN SKIN FOLLOWING XYLOL APPLICATION. R.K. Reed and S.A. Rodt* Department of Physiology, University of Bergen, Årstadveien 19, N-5009 Bergen, Norway.

We recently reported that in burn injuries IFP in skin falls to -100 to -200 mmHg (Lund, Wiig & Reed, Amer. J. Physiol. 255, H1049, 1988) explaining the rapid edema formation in this situation. We now report on a similar mechanism in the edema formation in the inflammatory rection caused by 2 min xylol application to skin. IFP was measured during the next 90 min with glass microcapillaries (tip diameter 3-5 μm) connected to a servocontrolled counterpressure system. Following xylol application, IFP fell from control pressures of -1.2 mmHg (SD= 0.7, n=7) to between -4 to -5 mmHg at 20 to 30 min after application and then returned to above control values as edema developed during the next hour. In order to abolish the edema that will mask the negativity of IFP, xylol was applied to the skin of another group of rats after circulatory arrest with intracardiac injection of saturated KCl. In this group IFP fell to between -10 to -15 mmHg during the first 20 min after xylol application, and remained at this level for the remaining time of the experimental period. The negativity of IFP following xylol application could not be prevented by pretreatment with indomethacin or a low dose of aprotinin. The increased negativity of IFP following xylol application will add directly to the normal capillary filtration pressure (0.5 to 1 mmHg) to greatly enhance the edema formation in the early phase following xylol application to the skin.

21.15

Flow Generating Properties of Mesenteric Collecting Lymphatics During Acute Increases in Lymph Formation **Joseph N. Benoit. Department of Physiology and Biophysics, L.S.U. Medical Center, Shreveport, LA**

Previous studies in mesenteric collecting lymphatics indicate that acute increases in lymph formation are met by an increased pumping efficiency of the lymphatic network. Increased lymph propulsion is due to elevations in lymphatic contraction frequency and stroke volume. However, the overall contribution of stroke volume and frequency in the movement of lymph during edematous conditions remains unclear. Therefore, the purpose of the present study was to analyze the flow generating capabilities of the lymphatic pump under resting conditions and during periods of enhanced lymph formation. The rat mesentery was prepared for microscopic observation and a collecting lymphatic selected for study. The preparation was transferred to a video microscope and lymphatic diameter and contraction frequency monitored. Following a 10 min control period, the rate of lymph formation was elevated by infusing isotonic saline into the femoral vein (2 ml/min/kg) for 45 min. Stroke volume and ejection fraction were determined for each contraction. During the first 20 minutes an increase in both diameter and frequency was observed. At periods of greater than 20 minutes, stroke volume but not frequency declined. Total lymph propulsion by the lymphatic pump tended to plateau since the reduction in stroke volume was proportionately greater than the increase in frequency. (Supp. by NIH-HL40963).

21.16

EFFECTS OF TRANSMURAL DISTENSION ON THE CONTRACTILE ACTIVITY OF ISOLATED RAT MESENTERIC COLLECTING LYMPHATICS. David C. Zawieja, Michael J. Davis, and Harris J. Granger, Dept. of Medical Physiology and Microcirculation Research Institute, Texas A&M University, College Station, TX. 77843

A collecting lymphatic from the rat mesentery (70-150 μm diameter) possessing intrinsic contractile activity was located in an exteriorized rat mesenteric preparation using a stereomicroscope. A section of tissue containing the vessel of interest was removed from the animal and placed in a chilled (4° C) buffer bath. There a section of lymphatic (2-3 lymphangions) was carefully dissected free of the surrounding tissue. Glass cannulas were then inserted and tied into the central and peripheral ends of the lymphatic. The vessel was pressurized at both ends to 2 cm H_2O and the temperature brought up to 35-37° C. After an equilibration period the isolated vessel resumed spontaneous contractile activity. The vessel was transferred to an inverted microscope equipped with a video camera and recorder. Experiments were recorded onto VHS tape. Lymphatic diameter was measured (10-20 hertz sampling rate) from the taped image over the course of the experiment. From the diameter record, contraction frequency, end diastolic diameter, end systolic diameter, stroke volume, ejection fraction, and lymph flow were calculated. These parameters were evaluated at the following distension pressures: 1, 2, 3, 5, 7 and 10 cm H_2O. The results of these isolated lymphatic studies paralleled results seen in previous intravital experiments. As lymphatic distension pressure increased the following effects were seen: 1) Contraction frequency increased and tended to reach a plateau when pressure was 5-7 cm H_2O; 2) Stroke volume increased until pressure reached 5 cm H_2O and then declined; 3) Calculated lymph flow increased until pressure reached 5 cm H_2O and then declined. Supported by NIH HL-38104, HL-21498 and AHA Texas Affiliate #G025.

21.17

ROLE OF XANTHINE OXIDASE IN POSTISCHEMIC GRANULOCYTE INFILTRATION AND MICROVASCULAR INJURY IN CANINE GRACILIS MUSCLE. RJ Korthuis, JK Smith, and DL Carden. Dept of Physiology, LSU Med Ctr, Shreveport, LA 71130.

Xanthine oxidase (XO) generated, oxidant-dependent granulocyte activation may play a role in the genesis of ischemia/reperfusion (I/R) injury. To assess the role of XO in I/R-induced neutrophil infiltration and microvascular injury in skeletal muscle, we examined the effect of XO depletion (using a tungsten-supplemented diet (W-diet), 0.7 g/kg diet), XO inhibition (using oxypurinol, 20 μM), and neutrophil depletion (<5% of control levels using antineutrophil serum, ANS) on granulocyte infiltration and the increase in microvascular permeability induced by 4 hr of ischemia and 30 min of reperfusion in canine gracilis muscle. In addition, we determined XO activities in muscle biopsies obtained at the end of the experiments. Changes in vascular permeability were assessed by determining the solvent drag reflection coefficient for total plasma proteins (σ) in the following groups: 1) 4.5 hr continous perfusion (non-ischemic); 2) I/R alone; 3) I/R+ANS; 4) I/R+W-diet; and 5) I/R+oxypurinol. Muscle neutrophil content was monitored by assessing tissue myeloperoxidase (MPO) activity in muscle biopsies obtained at the end of the experiments. In non-ischemic muscles, σ and muscle MPO averaged 0.96±0.04 and 0.7±0.5 U/g, respectively. I/R was associated with a marked increase in microvascular permeability (σ=0.64±0.02) and muscle MPO (18.4±4.7 U/g) that was attenuated by ANS (σ=0.99±0.05). Neither XO nor xanthine dehydrogenase were detected in biopsies obtained from gracilis muscles after 4 hr of ischemia. However, immunolocalization studies suggest that this enzyme is found only in capillary endothelial cells in skeletal muscle. Thus, XO may not be present in sufficient quantities in whole muscle homogenates to be detected by our assay but may be present in endothelial cells at levels sufficient to produce microvascular injury. Although XO depletion or inhibition attenuated the postischemic increase in muscle MPO (9.8±3.0 and 6.3±1.6 U/g, respectively), these interventions failed to ameliorate the I/R-induced increase in microvascular permeability (σ = 0.53±0.05 and 0.53±0.08, respectively). These results suggest that I/R-induced microvascular injury is neutrophil-dependent and that XO depletion or inhibition reduced the influx of granulocytes into postischemic muscle by at least 50%. However, the decrement in neutrophil influx associated with XO depletion or inhibition was insufficient to prevent postischemic microvascular injury.

21.18

MODEL FOR STUDYING INTESTINAL VASCULAR RESPONSES TO CHRONIC VASCULAR OCCLUSION. J.L. Unthank, M.C. Dalsing,* S.G. Lalka,* and D.F. Cikrit.* Departments of Surgery and Physiology and Biophysics. Indiana University School of Medicine, Indianapolis, IN 46202.

The technique recently described for repeated observation of the exact same intestinal microvessels (Unthank and Bohlen, Circ. Res. 61:616-624, 1987) has been utilized to develop a model for studying intestinal vascular responses to chronic vascular occlusion. The entire vasculature from branches of the superior mesenteric artery and vein to the arterioles, venules, and capillaries of the intestinal submucosal and muscle layers can be repeatedly observed over a period of weeks to months. With careful microsurgical technique and extreme care in handling the bowel, the experimental procedures do not cause adhesions or any apparent morbidity. Localized, graded reductions in arterial pressure or elevation of venous pressure are possible by varying the number of arterial or venous ligations. After ligation, the collateralization process can be studied using intravital microscopy techniques to measure numbers and diameters of vessels and blood pressure and flow. Ligation of the intestinal arteries in the mesentery permit collateral flow to occur through both extramural and intramural (microvascular) pathways. With ligation of the marginal artery between adjacent intestinal arteries, flow enters the collateral dependent region through the intramural arterioles and then re-enters the marginal artery. The greatest degree of enlargement of existing collateral vessels occurs in these intramural arterioles after marginal artery occlusion.

21.19

DIABETES ENHANCES ARTERIOLAR CONSTRICTION TO SEROTONIN IN STRIATED MUSCLE. N.L. ALSIP, L.S. UNGER* AND P.D. HARRIS, Dept of Physiology, Univ of Louisville, Louisville, KY 40292

Serotonin (5-HT) constricts large arterioles (>50μm) and dilates small arterioles (<50μm) in striated muscle. This study assessed this response in streptozotocin (STZ) treated rats. The microvascular experiment was performed in three treatment groups: a control, a STZ-low dose (40 mg/kg STZ, 1 week prior) and a STZ-high dose group (100 mg/kg STZ, 2 weeks prior). In anesthetized rats, the cremaster muscle (with intact nerve and blood supply) was suspended over an optical port in an environmentally controlled tissue bath. Arterioles were observed via closed-circuit television microscopy while 5-HT was added to the bath in sequential doses. Papaverine was applied to give maximal diameter. Data for large arterioles (A1) are reported as percent change from baseline. Data for small arterioles (A3 and A4) are reported as percent of the maximal dilation (max diameter minus baseline diameter). * statistically different from control, p<0.05.

	Blood Glucose	Response to 10-4 M 5-HT		
	mg/dl	A1	A3	A4
Control (n=5)	80-100	-39±3	69±8	78±3
STZ-low (n=6)	140-180	-44±3	39±7*	21±9*
STZ-high (n=5)	200-800	-55±4*	54±12	30±12*

5-HT induced constriction was enhanced in A1's of the STZ-high group, while small arteriolar dilation was blunted in both STZ groups. STZ-induced diabetes appears to enhance the constrictor action of 5-HT and blunt its dilator actions.

MECHANICS OF BREATHING: AIRWAYS

22.1

HYPERPNEA-INDUCED BRONCHOCONSTRICTION (HIB) AND BRONCHOVASCULAR HYPERPERMEABILITY (BVH) SHARE A COMMON INCITING STIMULUS IN GUINEA PIGS

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Isocapnic hyperventilation of dry gas (IHDG) elicits both HIB and BVH in guinea pigs. Guinea pig HIB depends largely upon tachykinin release from airway sensory nerves, as animals depleted of tachykinins by capsaicin pretreatment exhibit markedly reduced HIB, but hyperpnea-induced BVH remains unaffected by capsaicin pretreatment. Thus, the effector portions of the pathogenic mechanisms leading to these responses differ. In the current study, we tested the hypothesis that earlier steps in these 2 mechanistic pathways are shared. Specifically, we compared the time courses of appearance of HIB and BVH during or after dry gas hyperpnea in 12 male Hartley guinea pigs. Respiratory system resistance (Rrs) was monitored in a body plethysmograph, and monastral blue (MB) (0.5 ml iv, 3% suspension) was given to stain hyperpermeable blood vessels. Six animals received 5 min IHDG followed by 3 min quiet breathing of humidified air, and were then sacrificed by exchange transfusion with normal saline (*Group 1*). Six additional animals received 5-10 min IHDG, followed by exchange transfusion during continued dry gas hyperventilation (*Group 2*). Four *Group 1* animals exhibited MB staining of the central airways and experienced 4.3±1.2 (SE) fold rise in Rrs. Two *Group 1* animals had no MB staining, and exhibited only minor (1.4±0.2 fold) elevation of Rrs. *Group 2* guinea pigs displayed neither MB staining nor bronchoconstriction. These results indicate that cessation of dry gas hyperpnea prompts the appearance of both HIB and BVH, and suggest that these airway responses share a common inciting stimulus. We speculate that the pathways that mediate these two responses may share additional common early steps. Supp. by NHLBI Grants HL02205, HL41009, and HL07432.

22.2

EFFECT OF VIP ANTISERUM ON NONADRENERGIC, NONCHOLINERGIC RELAXATION OF CAT TRACHEALIS MUSCLE.

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The identity of the neurotransmitter(s) mediating nonadrenergic, noncholinergic (NANC) bronchodilation is still controversial. Vasoactive intestinal peptide (VIP) has been implicated, however, the lack of a reliable VIP antagonist has made it difficult to confirm a role for this peptide. We studied the effect of a specific VIP antiserum on NANC relaxation of cat tracheal smooth muscle in vitro. Adult cat tracheae were incubated overnight at 4°C in Krebs-Ringer solution containing a 1:100 dilution of VIP antiserum or normal rabbit serum. Tracheal rings were suspended between platinum stimulating electrodes in organ baths containing Krebs-Ringer solution at 37°C. After equilibration, propranolol (10μM) and atropine (1μM) were added to the baths and muscle tone was increased to 60-80% maximal with serotonin (0.3-0.7μM). Electrical field stimulation (EFS) was applied for ten second periods (0.2 msec,0.4 A) at 2-20 Hz. Frequency-dependent relaxation occurred in all tissues, with near maximal relaxation at 15 Hz. The response to EFS was not different in tissues incubated with VIP antiserum compared to controls (P > 0.05). At 20 Hz, EFS reversed serotonin-induced tone by 60.1 ± 8.5 % (sem) in tissues incubated with VIP antiserum (n = 9), and 74.5 ± 8.4 % in control tissues (n = 8). These findings argue against a critical role for VIP in NANC bronchodilation in the cat.

22.3

CARDIOSELECTIVE ACTION OF THE MUSCARINIC ANTAGONIST AF-DX 116 IN THE NEWBORN DOG. Kristy L. Brundage and John T. Fisher. Depts. of Physiology & Anaesthesia, Queen's University, Kingston, Canada K7L 3N6

Muscarinic M2 receptors are subdivided into $M2_\alpha$ and $M2_\beta$ subtypes that are associated with cardiac tissue and airway smooth muscle respectively. Although $M2_\alpha$ antagonists such as AF-DX 116 inhibit bradycardia, AF-DX 116 sensitive receptors have also been reported on smooth muscle (Arch. Pharmacol.335:593,1987). In assessing the functional status of muscarinic receptors in the newborn, we studied the dose-response effects of AF-DX 116 on vagally induced bradycardia and bronchoconstriction in the dog. Anesthetized, tracheostomized newborn dogs (2-4 days) were ventilated with the chest open and placed in a flow plethysmograph. The vagus nerves were stimulated supramaximally at 6 and 15/s. The % increase in lung resistance (RL) and decrease in heart rate (HR) during stimulation was measured after cumulative log dose increments of AF-DX 116. The dose required to inhibit 50% of the control RL response (ED_{50}) was ~ 10 times greater (range 6 to 40) than the ED_{50} for HR. At 10 μmol/kg AF-DX 116 90 % inhibition of the HR response was obtained compared to ~ 60 % for RL. We conclude that AF-DX 116 selectively inhibits the cardiac response to vagal stimulation in the newborn dog and that differentiation of M2 receptors has occurred in utero. $M2_\alpha$ receptors do not appear to mediate airway smooth muscle contraction in the newborn dog.

22.4

THE EFFECT OF VAGOTOMY ON AIRWAY RESISTANCE INDUCED BY ELEVATED LEFT ATRIAL PRESSURES IN DOGS. Edward Mezic, Naipaul Rambaran†, Kishore Ratkalkar, Sal Zabbatino†, Pierre Wolfe, Seethapathy Muralidharan†, John Nicewicz, David Murphy. Deborah Heart & Lung Center, Browns Mills, NJ 08015

We studied the effect of vagal innervation on airway resistance. Ten dogs were placed on cardiopulmonary bypass and a peripheral airway catheter was inserted via the trachea through the lung and connected to a pressure transducer. The left atrial pressure (LAP) was increased sequentially and central and peripheral resistance measured. The LAP was then lowered to the baseline value and after vagotomy, the procedure was repeated. The following results were obtained, 7 of 9 dogs showed a statistically significant increase in peripheral airway resistance (PAR) with increasing LAP($P<.05$). One dog showed this trend but was not statistically significant. Post vagotomy 7 of 8 dogs showed the same trend as above ($P<.05$). In the trachea, 6 of 8 dogs showed an increase in resistance with increasing LAP, 4 of which were statistically significant ($P<.05$). Post vagotomy did not show this trend. From this we conclude that increasing LAP caused an increase in PAR and vagotomy did not effect this, suggesting absence of any significant parasympathetic effect. Although central resistance also seemed to increase with increasing LAP prior to vagotomy, this trend was not appreciated post vagotomy.

22.5

AIRWAY CLOSURE CAUSED BY METHACHOLINE IN LIVING DOGS. D.O. Warner* and S.J. Gunst. Departments of Anesthesiology and Physiology and Biophysics, Division of Thoracic Diseases and Internal Medicine, Mayo Clinic and Foundation, Rochester, MN 55905.

The response of pulmonary resistance (R_L) to increasing doses of methacholine (MCh) exhibits a plateau at higher drug doses in several species, suggesting that bronchoconstriction in vivo is limited. We have demonstrated in excised canine lobes that airways close in response to high doses of MCh at transpulmonary pressures (P_L) of $\leq$ 7.5 cm H_2O (JAP 65: 2490-2497, 1988), suggesting that the plateau in the dose-response curve is not caused by interdependence between airways and the lung parenchyma. We studied whether neurohumoral or systemic factors in vivo might prevent the airway closure seen in excised lungs. The R_L response to increasing doses of MCh was first measured in 6 dogs. The relationship between MCh dose and R_L response consistently exhibited a plateau at low values of R_L. At least one week later, the left lung was ventilated to maintain hyperoxia and normocapnia while MCh was nebulized into the airways of the right lower lobe held at P_L ranging from 25 to 5 cm H_2O. Airway closure was assessed by comparing changes in alveolar pressure (measured by an alveolar capsule technique after sternotomy) and airway opening pressure during small amplitude oscillations in lobar volume. The airways always closed at $P_L \leq 7.5$ cm H_2O. In conclusion, we found no evidence of mechanisms that prevent airway closure at $P_L \leq 7.5$ cm H_2O when MCh is nebulized into the airways of single lobes in living dogs under static conditions. (Supported by HL-29289 and GM/HL-40909.)

22.6

AGONISTS OF AIRWAY SMOOTH MUSCLE (ASM) CONTRACTION MAY PREVENT AIRWAY COLLAPSIBILITY IN TRACHEOMALACIA (TM). H. Panitch, E. Keklikian*, and technical assistance of R. Motley*. St. Christopher's Hosp. for Child., Temple Univ. Sch. of Med., Phila., Pa. 19133.

We have observed several infants with TM who have developed signs of increasing airway obstruction after bronchodilator (BD) therapy. This finding prompted us to study the effects of of cholinergic and BD agents on airway mechanics in infants with TM using the thoraco-abdominal compression technique. The following 5 mo infant with documented TM is illustrative. $\dot{V}$maxFRC was measured at baseline and after inhalations of normal saline and increasing concentrations of methacholine (MCh). MCh concentrations were increased until two successive dilutions showed no change in $\dot{V}$maxFRC. At baseline, the $\dot{V}$maxFRC was 35 ml/sec. Administration of 0.3 mg/ml MCh increased $\dot{V}$maxFRC to 77 ml/sec (119% over baseline). The $\dot{V}$maxFRC dropped to baseline values after administration of 5mg nebulized albuterol (Alb). Bethanechol Cl 2.9mg/M^2 q8 hr was given for 10 days, after which the $\dot{V}$maxFRC was 60 ml/sec. Administration of Alb resulted in a decrease in the $\dot{V}$maxFRC of 39%. These findings suggest that 1) agonists of ASM contraction may prevent airway collapse by making the airway less compliant, and 2) BD's may increase airway collapse in patients with TM.

22.7

EVALUATION OF FLOW-VOLUME LOOPS DURING BREATHING OF 8, 10 AND 12% CO_2/AIR MIXTURES IN HORSES. D.B. Tesarowski, L. Viel* and W.N. McDonell*. Clin. Studies, OVC, Guelph, ON, N1G 2W1.

The present study was designed to characterize the effects of different CO_2/air mixtures on parameters measured from flow-volume loops in unsedated horses. The objective was to evaluate which mixture is best suited to increase ventilation as a simulation of the forced vital capacity maneuver used in human medicine. Each of 4 horses were randomly challenged with each test gas (8,10 12% CO_2/in air) on successive days. Parameters which were recorded at baseline and repeated at 2,4,6, and 8 min of challenge included inspired tidal volume, respiratory rate, minute ventilation, inspiratory and expiratory times ($T_{i,e}$), peak inspiratory and expiratory flow rates, expiratory flow rate at 25 and 50% tidal volume, and expired volumes at 0.5, 0.75 and 1 sec. Each test gas significantly increased ($p < 0.05$) the above parameters with respect to baseline with the exception of T_i and T_e which were significantly decreased. Generally, the increase (or decrease) observed caused by the 8% CO_2/air mixture was significantly less than that observed for the other two test mixtures. Although maximal changes from baseline were usually observed at 8 min, there were no significant changes between 2 successive time blocks after 4 min. Since parameters recorded during inhalation of the 10% or 12% CO_2/air mixture were qualitatively and quantitatively the same, we conclude that either gas mixture may be used to increase ventilation. However, gas should be inhaled for at least 4 min.

22.8

EFFECT OF VASCULAR VOLUME EXPANSION ON THERMALLY INDUCED AIRWAY OBSTRUCTION. J.A. Gilbert*, C.J. Winslow*, K.A. Lenner*, J.A. Nelson*, and E.R. McFadden Jr. Case Western Reserve University, Cleveland, Ohio 44106.

It has been suggested that the bronchial circulation may play a pathogenetic role in the development of airway obstruction to thermal stimuli such as exercise and hyperventilation. To provide more data on this phenomenon, we expanded the vascular volume of 8 asthmatic a 8 normal individuals with intravenous saline (30ml/kg). We then imposed a thermal stimulus on the bronchial microvasculature by having each subject hyperventilate (HV) before and during the infusions. In the asthmatics, saline (S) and HV produced equivalent obstruction ($\max\Delta FEV_1$ S=0.65±0.16, HV=0.57±0.10L) In the normals, both stimuli produced much smaller effects, but S resulted in greater obstruction than HV (ΔFEV_1 S=0.33±0.05, HV=0.09±0.01L). In the asthmatics, when the vessels had been pre-stimulated thermally, fluid administration greatly amplified the resulting obstruction, and the fall in FEV_1 was double that seen with either S or HV alone (ΔFEV_1= 1.18±0.26L). Giving fluid before HV markedly attenuated the response to the latter (ΔFEV_1=0.37±0.18L). In the normals, this combination of events produced the same general pattern, but on a smaller scale. Our data suggest that HV in asthmatics is associated with capillary leakage and that this phenomenon can be greatly exaggerated by vascular volume expansion. They also demonstrate that prior volume expansion attenuates the response to thermal stimuli. The mechanism for the latter phenomenon may be related to changes in the degree of airway cooling which develops during hyperpnea, the rate of airway rewarming post-hyperpnea, or the gradient between them.

22.9

EFFECT OF VOLUME HISTORY IN ALLERGEN-INDUCED ASTHMA.
V. Brusasco, R. Pellegrino*, B. Violante*, and E. Crimi*. Università di Genova, 16132 Genova, and Ospedale A. Carle, 12100 Cuneo. Italy.

We studied 9 patients with biphasic asthmatic reaction to inhaled allergen. To quantitatc the effect of deep inspiration (DI) on induced bronchial obstruction we compared the maximal expiratory flow at 40% of vital capacity (MEF_{40}) from partial (P) and maximal (M) expiratory flow-volume curves, and airway specific conductance before (sGaw) and after DI ($sGaw_{DI}$). At beseline, the ratio $MEF_{40}M/P$ was 1.44 ± 0.32 (SD) and the ratio $sGaw_{DI}/sGaw$ 0.94 ± 0.15. During early phase asthmatic reaction (EAR), $MEF_{40}M/P$ was 2.61 ± 0.66 and $sGaw_{DI}/sGaw$ 1.95 ± 0.53. These ratios were significantly ($p < 0.001$) different from baseline. During late phase asthmatic reaction (LAR), when absolute sGaw values were similar to those during EAR, $MEF_{40}M/P$ was 1.85 ± 0.47 and $sGaw_{DI}/sGaw$ 1.39 ± 0.26. These ratios were significantly different from those at baseline ($p < 0.05$) and during EAR ($p < 0.01$). We conclude that DI has a more pronounced bronchodilator effect during EAR than during LAR. This difference may be explained with a different balance between airway and parenchymal hysteresis under these two conditions.

22.10

END-TIDAL TEMPERATURE DURING HYPERVENTILATION OF DRY AIR IN ASTHMATIC AND HEALTHY SUJECTS. Jacques Regnard, Majed Beji*, Jean-François Dessanges*, Alain Lockhart. Laboratoire de Physiologie, CHU Cochin, 75014 Paris, France.

We recorded end-tidal expiratory temperature (TE) during isocapnic hyperventilation (IHV) of dry air at room temperature (19-22°C) and recovery in 7 healthy (HS) and 10 asthmatic subjects (AS). After baseline determination on room air, TE was measured on dry air 4 times per min, at 4 levels of ventilation (10, 20, 40, 80% of maximal voluntary ventilation = FEV1x30) lasting 3 min and separated by 3 min intervals. The results were: 1)TE at the end of each ventilation step decreased in both AS and HS but was slightly higher at the end of challenge in AS than in HS (24.5°C and 23.3°C respectively, $p<0.001$); 2)whereas TE remained constant or decreased in HS at all levels of ventilation and in AS at 40 and 80% of MVV, it rose after a transitory fall during the 2 lowest ventilation steps in AS; 3)during recovery of IHV, TE rose faster in AS than in HS, as already found with in-situ measurements of airway temperature (Gilbert JAP,64:2167, 1988). Our results suggest that airway mucosal blood flow increases during dry air challenge in asthmatic subjects.

22.11

CLEAVAGE PRODUCTS FORMED WHEN SUBSTANCE P AND NEUROKININ A ARE OFFERED TO THE LUNG VIA THE AIRWAYS. M.A. Martins, S. Shore, N. Gerard*, C. Gerard* and J.M. Drazen. Dept. Med. Beth Israel Hospital, Boston, Massachusetts 02215.

The role of neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE) in the degradation of substance P (SP) and neurokinin A (NKA) when these peptides are presented to the lung via the airway surface was examined using ^{3}H-Prolyl^{2,4}SP and ^{125}I-Histidyl^{1}NKA as markers. Lungs were perfused with buffer or buffer with thiorphan 1 uM or captopril 3 uM. The perfusate collected after infusion of SP or NKA was resolved by HPLC; identity of metabolites was determined by co-chromatography with known standards. In the absence of thiorphan and captopril, the major cleavage products recovered after SP infusion co-chromatographed with SP 1-9, SP 1-7, SP 1-6 and the dipeptides Arg-Pro and Lys-Pro. After NKA infusion products co-chromatographed with methoxy-NKA, NKA 1-8, NKA 1-5 and the dipeptide His-Lys. NEP inhibition resulted in an increase in the recovery of SP 1-11 and a decrease in the formation of SP 1-7 and SP 1-6. After NKA infusion, NEP inhibition resulted in an increase in the recovery of NKA 1-10 and a significant ($p < .05$) decrease NKA 1-8 and NKA 1-5. ACE inhibition had no effect. These results are consistent with NEP but not ACE cleavage of both SP and NKA when these peptides are presented to the lung via the airways. Supported by HL 39827 and CNPQ-BRAZIL (MAM).

22.12

EFFECTS OF A POTENT LTD$_4$ ANTAGONIST, MK-571, ON AIRWAY INFLAMMATION DURING LATE RESPONSES TO ANTIGEN CHALLENGE IN THE RAT. **S. Sapienza*, P. Renzi*, D.H. Eidelman and J.G. Martin. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, H2X 2P2, Canada.**

The purpose of this study was to examine the effects of MK-571, a potent LTD$_4$ antagonist, on changes in pulmonary resistance (R_L) and inflammatory cells within the bronchoalveolar compartment during the late response to inhaled antigen. We studied 30 male Brown-Norway rats, 7 to 8 weeks old and 190 to 220 g in weight, which were actively sensitized to ovalbumin (OA). Fourteen days after sensitization rats were anesthetized with urethane (1.1g/kg) and intubated endotracheally. Seven rats were challenged with aerosolized saline and used as control (A). 10 rats were challenged with aerosolized OA (50 mg/ml in saline) (B). Six rats were challenged with OA and were treated with MK-571 (bolus of 1 mg/kg I.V. and infusion of 25 ug/kg/min in saline) before OA (C) and another 6 received MK-571 at 2 hrs after OA (D). BAL was performed at 10 hrs after OA. A LR was observed in 6 of 10 rats of B, but no LR occurred in C and D. BAL showed a significant difference among groups in total cells ($p<0.05$). Lymphocytes and neutrophils increased significantly in B, C and D. There was no significant change in eosinophils. Despite inhibition of the LR, MK-571 did not alter BAL findings. (Supported by M.R.C. Canada.)

22.13

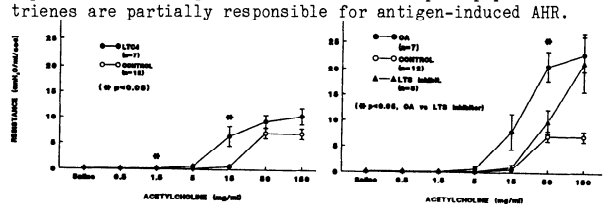
UPPER AIRWAY LATE RESPONSES OF SENSITIZED RATS TO ANTIGEN PROVOCATION. **L. Xu,* D.A. Eidelman, J.H.T. Bates and J.G. Martin. Meakins-Christie Laboratories, McGill University, Montreal, H2X 2P2.**

Late pulmonary responses following antigen challenge of awake small animals have been reported. To determine the contribution of the upper airway to the changes in respiratory resistance during the late response (LR) to antigen provocation, we studied the magnitude and time course of changes in upper airway resistance (Ru) of sensitized Brown-Norway rats from 5 to 10 hours after aerosol challenge with ovalbumin (OA). Two weeks after sensitization animals were challenged by inhalation through the nose. Airway responses of 8 OA challenged animals were compared to those of 7 animals challenged with saline. Seven of 8 rats in the experimental group had increased upper airway resistance and also displayed LR. Ru during expiration was highly alinear so that analysis was confined to Ru during inspiration (Ru,insp). Ru,insp was 1.262±0.09 cm H_2O/ml/sec (mean ±SE), which was 2.6 times the value for saline challenged animals (0.476±0.143 cm H_2O/ml/sec) and reached a peak value of 3.454±0.45 cm H_2O/ml/sec. The time to peak was 446±37.3 min after OA challenge. The duration of the LR in the upper airway was 146±34.9 min. We conclude that inhalation of antigen through the upper airway of the sensitized rat results in a substantial increase in upper airway resistance and a distinct LR. (Supported by M.R.C. Canada.)

22.14

ROLE OF LEUKOTRIENES IN AIRWAY HYPERRESPONSIVENESS (AHR) IN GUINEA PIGS (GP). K. Ishida and R.R. Schellenberg. UBC Pulmonary Research Lab., Vancouver, B.C.

Changes in pulmonary resistance (R_L) to inhaled acetylcholine (Ach) 3 days after the last aerosol challenge were measured in 4 groups of GP receiving repeated aerosol challenges (2/wk x 5wk) with: 1) LTC_4 10^{-6}M in .05% GP albumin (n=7), 2) .05% GP albumin controls (n=12), 1% ovalbumin (OA) in OA-sensitized GP (n=7), 4) 1% OA after leukotriene synthetase inhibitor (LTS inhibit) L-663,536 3mg/kg p.o. (Merck). Repeated OA aerosol (● , R graph) produced a left shift in the Ach dose-response and increased maximal R_L. LTC_4 (● , L graph) caused a left shift without increased maximal response, whereas the LTS inhibit (▲) blocked the left shift, but not the maximal R_L, produced by repeated OA challenge. We conclude that sulphidopeptide leukotrienes are partially responsible for antigen-induced AHR.



22.15

BRONCHOCONSTRICTION ELICITED BY PLATELET ACTIVATING FACTOR (PAF) IN ISOLATED RAT AIRWAYS PERFUSED WITH PLATELET-FREE SOLUTION. N.M. Munoz*, C. Tutins*, and A.R. Leff. Sect. Pulm. & Crit. Care Med. and Comm. Clin. Pharmacol., Division of the Biol. Sci., Univ. Chicago, Chicago, IL 60637.

The mechanism by which PAF elicits bronchoconstriction is complex and involves both platelet and neuronal activation. To determine if PAF also has a direct action on airway smooth muscle, we studied the effect of PAF in isolated bronchial circulation (BC) and pulmonary circulation (PC) of 30 blood free Sprague-Dawley rats using an in situ perfusion method that we have reported previously [J. Appl. Physiol. 66:203-209, 1989]. Dose-response curves were generated with 10^{-10} to 10^{-7} mol PAF dissolved in Krebs solution containing 4% albumin in the presence or absence of the PAF-antagonist, CV-6209. In the BC, intra-arterial PAF caused dose-related increase in lung resistance (Rl) from 1.09 ± 0.3 to 1.92 ± 0.16 mm H_2O/ml/s ($p < 0.05$) and from 1.07 ± 0.2 to 1.68 ± 0.9 mm H_2O/ml/s in the PC ($p < 0.05$). Bolus injection of 10^{-6} mol CV-6209 + 10^{-7} mol PAF caused 78% inhibition of the maximal Rl response; addition of atropine, methysergide or chlorpheniramine had no effect. The same dose of CV-6209 inhibited completely the response to PAF in the PC. There was complete tachyphylaxis in both BC and PC to PAF in repeat dose-response studies in the same animals. In separate cumulative dose-response studies, addition of 10^{-6} mol CV-6209 to the BC perfusate caused 87% inhibition of the RL response to PAF and 100% inhibition in the PC. We find that PAF causes bronchoconstriction in blood free rat airways. PAF appears to have a direct action on airway smooth muscle predominantly in the central airways. [Supported by NHLBI grants HL-32495, HL-35718, HL-01398].

22.16

TOLUENE DIISOCYANATE (TDI) STIMULATES THE EFFERENT FUNCTION OF CAPSAICIN-SENSITIVE SENSORY FIBERS. CE Mapp, P Chitano*, LM Fabbri, R Patacchini*, S Giuliani* and CE Maggi*. Institute of Occupational Medicine, University of Padua, Padua, A Menarini Plc, Florence, Italy.

Isocyanates are an important cause of occupational asthma. The mechanism of isocyanate-induced asthma is still unknown. Tachykinins may play a role in TDI-induced asthma. Thus, to determine whether TDI stimulates the "efferent" function of peripheral endings of capsaicin-sensitive sensory nerves, we investigated the effect of TDI in the rat isolated urinary bladder. TDI (0.03-3 mM) produced a concentration-dependent contraction of the bladder strips. Previous exposure of the strips to capsaicin followed by washing out produced a complete unresponsiveness both to TDI and to a second exposure of capsaicin. The response to both TDI and capsaicin was completely prevented by extrinsic bladder denervation, achieved by bilateral removal of pelvic ganglia (72 h before). These experiments provide the first evidence that TDI activates, directly or indirectly, the "efferent" function of capsaicin-sensitive primary sensory neurons. Further studies are necessary to establish whether a similar effect occurs in the airways and it might play a role in TDI-induced asthma.

22.17

THE EFFECTS OF A LEUKOTRIENE (LT) D_4 ANTAGONIST (MK-571) ON LTD_4 AND ANTIGEN-INDUCED BRONCHOCONSTRICTION IN ALLERGIC SHEEP. W.M. Abraham, A. Ahmed*, and A. Cortes*. Pulmonary Div., Mt. Sinai Medical Center, Miami Beach, FL 33140.

The effects of the LTD_4 receptor antagonist MK-571 (Can J Physiol Pharm 67:17, 1989) on LTD_4-induced bronchoconstriction and antigen-induced early and late responses were studied in allergic sheep. Specific lung resistance (SR_L) was used to measure the airway response to the inhaled agents. MK-571 delivered by MDI at doses of 5000, 2500 and 500 μg caused dose-dependent protection against LTD_4-induced bronchoconstriction (84, 58 and 43% protection [n=5], respectively). This effect was maximal with a pretreatment time of 30 min, but began to disappear by 4 hr. In the control trial (n=7) inhalation challenge with Ascaris suum caused early and late increases in (mean±SE) SR_L over baseline of 278±21% and 109±8%, respectively. MK-571 (5000 μg) given 30 min before and 4 h after challenge, did not significantly affect the severity of the early response 209±28%, but caused it to reverse more rapidly and blocked the late response (31±8%, P<.05 vs control). Our findings suggest that LTD_4 influences the duration of the early antigen-induced bronchoconstriction and plays a role in the late response. We previously found that MK-571 does not block airway hyperresponsiveness at the time of the late response (even though the late response, per se, is blocked). This suggests that although LTD_4 is a mediator of the late bronchial obstruction, its role in the development of airway hyperresponsiveness during the late response may be limited. Supp: NIH HL-33897.

22.18

ATTENUATION OF AIRWAY REACTIVITY TO OVALBUMIN (Oa) ANTIGEN CHALLENGE IN SENSITIZED GUINEA PIGS BY FUROSEMIDE AND AMILORIDE. Dale R. Bergren, Robert G. Townley* & Virginia A. Bergren. Omaha, NE 68178

Bianco et. al. (Lancet 1988) reported that furosemide protected against exercise induced asthma. To further study the mechanism we challenged sensitized guinea pigs with aerosols of Oa (0.5% & 0.1% w/v) with or without pretreatment of furosemide (0.25% w/v) or amiloride (0.1%) respectively. For 10 minutes after the antigen challenge, specific airway resistance (SRaw) was monitored via a whole-body plethysmograph (Model P, Buxco) which was connected to a respiratory analyzer (Buxco). Oa increased SRaw at all times and with both doses (N=8/group). Furosemide and amiloride aerosols attenuated the effect of Oa in these unanesthetized guinea pigs. The action of amiloride may be to inhibit Na+ influx into the airway smooth muscle cell, thereby reducing its contraction. This study supports the possible beneficial action of "loop diuretics" and amiloride in the treatment of asthma.

22.19

THE EFFECT OF INHALED FUROSEMIDE ON METHACHOLINE AND COLD AIR HYPERVENTILATION CHALLENGE BRONCHIAL RESPONSE. R.E. Grubbe, R.J. Hopp, N. Dave, B Brennan, AK Bewtra, RG Townley. Creighton University, Omaha, NE 68178

Inhaled furosemide (F) has been shown to inhibit the bronchoconstrictive effects of exercise, ultrasonically nebulized water and antigen challenge. The mechanism of action of these challenges (except antigen challenge) is thought to be a change in the osmolarity of the fluid surrounding the bronchial mucosa with mast cell degranulation. We report our findings of the effect of inhaled F on cold air hyperventilation challenge (CAHC) and methacholine challenge (MC). We studied 10 asthmatics in a double-blind, placebo-controlled crossover study. Each subject performed a CAHC. A minimum drop of 15% from baseline FEV1 was required for entry. On day 2, the subjects inhaled 20 mg. of F (2.8 ml.), and a FEV1 was determined for one hour post-F. Days 3 and 4 included placebo (P) or F, followed by CAHC. Days 5 and 6 included P or F followed by MC. Our results show F alone did not affect FEV1 in the hour after inhalation. The baseline FEV1s show no statistically different daily variation. There is no difference between P or F on the dose of methacholine causing a 20% fall in FEV1. Inhaled F significantly attenuates the bronchoconstrictive effect at 6 and 9 minutes post CAHC (p = <.05, and .029 respectively) when compared to P and approached significance at 12 and 15 minutes post CAHC (p = <.052 and .056 respectively) These results show inhaled F attenuates CAHC.

22.20

EFFECT OF KETOTIFEN ON BETA-ADRENERGIC RESPONSES IN GUINEA PIG AIRWAYS. T.A. Townley, D.K. Agrawal, T. Koshino, R.G. Townley. Creighton University, Omaha, NE 68178

We examined the effect of Ketotifen on beta-adrenergic responses in guinea pig airway tissues. Tracheal rings were constricted with 10uM methacholine followed by a dose-response curve to isoproterenol (ISO). Preincubation of the trachea with 1uM terbutaline at 37 C for 1 hour decreased the potency of ISO to produce relaxation by about 10 x. Ketotifen prevented the tachyphylaxis to ISO in a dose-dependent manner. At 1um ketotifen, the EC50 values of ISO before and after terbutaline exposure were not significantly different. Ketotifen alone increased the potency of ISO. These functional studies were also supported by radioligand binding studies. Ketotifen prevented the down-regulation of beta-adrenoreceptors induced by terbutaline in guinea pig lung and spleen. These data suggest that ketotifen might be helpful in preventing the beta-adrenergic tachyphylaxis and could be used in the prophylactic treatment of asthma.

22.21

REACTIVITY OF GUINEA PIG ISOLATED PERFUSED TRACHEA IN RESPONSE TO SEROSAL OR MUCOSAL EXPOSURE TO ACETYLCHOLINE (ACh), METHACHOLINE (MCh) AND CARBACHOL (CCh). J.S. Fedan and D.G. Frazer. Physiol. Sect., NIOSH, Morgantown, WV 26505

The influence of the mucosa on the reactivity of tracheal smooth muscle to cholinergic agonists was assessed by comparing pressor (contractile) responses of the perfused trachea (Munakata et al., J. Appl. Physiol. 64:466, 1988) to the serosal, extraluminal (EL) or mucosal, intraluminal (IL) application of ACh, MCh and CCh. When first applied EL and then IL, ACh, MCh and CCh were substantially more potent EL than IL; respective EL and IL mean EC_{50} (M) values (n = 4) were: $2.6x10^{-6}$ and $4.3x10^{-4}$ for ACh, $7.0x10^{-7}$ and $4.8x10^{-4}$ for MCh, and $1.3x10^{-7}$ and $7.6x10^{-5}$ for CCh. IL/EL EC_{50} ratios were 259, 814 and 625 for ACh, MCh and CCh, respectively. The maximum responses (cm H_2O) to IL ACh and MCh were smaller than EL responses (ACh: 2.8 and 8.0; MCh: 5.0 and 12.8; IL and EL, respectively), whereas the maxima for CCh were comparable (7.4 and 8.5, IL and EL, respectively). Similar findings were seen when the drugs were first added IL. The smaller maxima in response to IL ACh and MCh suggest that, in addition to being a significant diffusion barrier, the epithelium releases in response to IL ACh and MCh an inhibitory factor, which exerts a physiological antagonism and reduces the efficacy of the drugs. The maximum IL CCh response is less affected because of its more potent direct effect on the smooth muscle.

22.22

MILD ASTHMATICS DO NOT SHOW TOLERANCE TO MULTIPLE REPEATED METHACHOLINE CHALLENGE TESTS. W.S. Beckett, P.E. Pace* and M. Marenberg*. Yale University School of Medicine and John B. Pierce Foundation Laboratory, New Haven, CT 06510.

Inhalation challenge with aerosolized methacholine is used to assess airway responsiveness (which may increase after breathing antigens or pollutant gases). However, repeated methacholine challenge in non-asthmatic subjects (who require higher doses of methacholine to produce a 20% decrease in FEV_1) produces diminishing methacholine responsiveness or tolerance (ARRD 137:1499, 1988). To determine whether this occurs in asthmatics as well, we studied eight young (mean age 27 years) mild asthmatics (occasional but not regular use of inhaled beta agonists, PC_{20} methacholine range 0.2-3.3 mg/ml) who underwent five methacholine challenges at 1-1/2 hour intervals. Doubling concentrations of methacholine were given until FEV_1 fell by 20%. The mean cumulative dose of methacholine producing a 20% fall in FEV_1 in the fifth challenge was not significantly different from the dose required in the first challenge. These results indicate that marked tolerance to methacholine does not occur in mild asthmatics with multiple repeated challenges over 6 hours. We speculate that the lower cumulative dose of methacholine required by asthmatics is insufficient to produce tolerance. Supported by NIEHS Clinical Investigator Award ES00131.

22.23

5-HYDROXYTRYPTAMINE POTENTIATES ELECTRICAL FIELD STIMULATION-INDUCED CONTRACTIONS OF ISOLATED RAT BRONCHI: INVOLVEMENT OF 5-HT_2 RECEPTORS. John L. Szarek, Nancy L. Schmidt* and Carl A. Gruetter*. Department of Pharmacology, Marshall University School of Medicine, Huntington, WV 25755-9310.

Corroborating previous reports in dogs and rats, we found that electrical field stimulation (EFS)-induced contractions of isolated rat bronchi were potentiated by 5-hydroxytryptamine (5-HT). Since acetylcholine-induced contractions were unaffected by 5-HT, it was concluded that 5-HT potentiated EFS-induced contractions by a presynaptic mechanism. The aim of this study was to characterize the presynaptic 5-HT receptors that mediate potentiation with the use of antagonists (10^{-7} M final concentration) selective for different 5-HT receptor subtypes. The 5-HT_3 receptor antagonists, MDL-72222 and ICS-205930, were without affect on the potentiating effects of 5-HT. Mianserin (5-HT_{1C} & 5-HT_2 antagonist) was capable of inhibiting the facilitating effects of 5-HT. Similarly, 5-HT_2 receptor antagonism with ketanserin abolished the potentiating effects of 5-HT on EFS-induced contractions. These results suggest that the facilitatory effects of 5-HT on contractile responses elicited by EFS of isolated rat airways are mediated by activation of 5-HT_2 receptors. (Aided by a grant from the American Lung Association to JLS).

22.24

THE "EFFECTIVE DOSE" CONCEPT IN OLDER ADULTS EXPOSED TO OZONE. D.M. Drechsler-Parks, S.M. Horvath and J.F. Bedi*. Institute of Environmental Stress, University of California, Santa Barbara, CA 93106

The magnitude of pulmonary function decrements induced by exposure to ozone (O_3) in young adults is related to the "effective dose" of O_3 inhaled. Effective dose = [O_3 concentration (ppm)] x [mean minute ventilation (V_E)] x [exposure duration (min)], the relative contributions of each to the development of pulmonary function decrements in older adults is unknown. Twelve healthy, non-smoking men and women (60-79 yrs) performed four experiments: (1) 1 hour continuous exercise, and (2) 2 hours intermittent exercise, in filtered air (FA), and 0.45 ppm O_3, resulting in different effective doses of O_3. Forced vital capacity, FVC, and associated calculated parameters were measured pre- and post-exposure. Ozone exposure induced decrements in forced expiratory volume in .5, 1 and 3 seconds (FEV_t) with both protocols, but there were no changes in FVC with any exposure. Forced expiratory flow rate at 25% and 50% of FVC and forced expiratory flow rate between 25% and 50% of FVC decreased with all exposures, suggestive of fatigue. Ozone exposure induced similar decrements in $FEV_{1.0}$ under both exercise protocols. The mean exercise V_E was 25.3 and 25.2 L/min for the continuous and intermittent exercise protocols, respectively. No physiologically significant metabolic changes occurred with any exposure. Ozone concentration contributed the most to the pulmonary function changes, followed by V_E, and exposure duration, the same relative rankings observed in young adults. (EPA R813049-010).

THE PULMONARY CIRCULATION: CELLULAR AND PHYSIOLOGIC RESPONSES

23.1

MATURATION OF PULMONARY INTRAVASCULAR MACROPHAGE FUNCTION IN NEWBORN LAMBS. KE Longworth, D Lei*, EL Schultz*, A Westgate*, MK Grady*, and NC Staub. Cardiovasc Res Inst, Univ of Calif, San Francisco, CA 94143-0130.

The presence of reactive pulmonary intravascular macrophages correlates closely with the hemo- and lymph dynamic responses to foreign particles in several species (SG&O 153:845, 1981; JAP 64:1143, 1988). To establish cause and effect, Koch's third postulate requires that, if there is a response when reactive macrophages are present, there be no response when they are absent in the same animal. Because the newborn piglet has few intravascular macrophages (MVR 33:224, 1987), we studied 6 lambs over 2 weeks after delivery. We measured the pulmonary arterial pressure change (ΔP_{pa}, cm H2O) after injecting 0.6 ml/kg 1% Monastral Blue dye or 111-In-labeled liposomes, when the lambs were 1-3 days or 1-2 weeks old. We killed two lambs at each age and assayed their lungs for 111-Indium. The table shows mean values.

Age, days:	1-3	7-8	14-15
Liposomes, ΔP_{pa}	1.1	9.5	9.0
Monastral Blue, ΔP_{pa}	1.0	14.5	21.8
Lung 111-In, % injected	17	22	53

Lambs had no response at 1-3 days but retained some 111-Indium in the lung. At 1-2 weeks lambs showed reactivity and increased lung 111-Indium. This natural experiment supports the view that intravascular macrophages are responsible for the pulmonary reactivity to foreign particles. [Supported by HL25816 (Prog Proj) & NRSA Fellowship (KEL)].

23.2

EFFECT OF METHYLENE BLUE AND CYCLOOXGENASE INHIBITON UPON VASCULAR REACTIVITY TO SEROTONIN IN THE DOG LUNG. W.F. Hofman, H. El Kashef* and I.C. Ehrhart. Medical College of Georgia, Augusta, GA 30912.

Recent evidence suggests that vasodilation induced by endothelium-derived relaxing factors (EDRF) is mediated via guanosine-3',5'cyclic monophosphate (cGMP). In the present study, methylene blue (MB), a putative inhibitor of guanylate cyclase, was given to clarify the role of EDRF in controlling vascular tone and modulating pressor responses to serotonin (5-HT) in the isolated dog lung. Lung lobes (n=6) perfused with autogenous blood at constant flow, were given bolus doses of 50, 100 and 250 ug 5-HT before MB (pre-MB), after infusion of 0.5 mg/min MB for 40 min (MB) and after cyclooxygenase inhibition (COI; 40 uM indomethacin) during MB infusion (COI+MB). Lobar vascular resistance (R_T) was partitioned into upstream (Ra) and downstream (Rv) segments by venous occlusion. MB infusion did not change base line R_T or the segmental distribution of R_T whereas MB+COI increased base line R_T 120% by nearly equal increases in Ra and Rv. The dose dependent increase in R_T to 5-HT was not altered by MB but was markedly increased after COI. The mean (±SE) change in R_T (cmH20/L/min) to each dose of 5-HT is presented below. * P< 0.05 from PRE-MB.

5-HT (ug)	PRE-MB	MB	MB+COI
50	25.6±2.7	37.1±5.3	66.5±11.7*
100	39.1±4.5	53.1±5.3	94.9±14.6*
250	51.9±5.5	73.7±6.5	119.5±17.7*

Our results suggest that vasodilator cyclooxygenase products are more important in maintaining a low R_T and in modulating pressor responses to 5-HT in the dog lung than are EDRFs. (Supported by HL 40488)

23.3

PULMONARY VASCULAR SMOOTH MUSCLE CELLS & PERICYTES IN CULTURE EXHIBIT DIFFERENTIAL RESPONSES TO SPECIFIC MITOGENS.

Paul Davies. Univ. of Pittsburgh Sch. Med., Pittsburgh, PA 15261

Common features of the vascular remodeling accompanying pulmonary hypertension are hypertrophy of the medial smooth muscle layer of conduit arteries and muscularization of previously nonmuscular peripheral arteries. Both changes involve proliferation of the effector cells - the vascular smooth muscle cell(SMC) and the pericyte(PC), respectively, yet little is known of the response of these two cells to mitogen stimulation. To study this, vascular smooth muscle cells were obtained from explants of the left intrapulmonary artery of adult male Sprague-Dawley rats; pericytes were obtained by collagenase digestion of peripheral lung tissue. The cells were grown in DME/F12 supplemented with 10% FBS. Under these conditions both cell types exhibited a similar morphology, often spreading widely on the plastic, displaying prominent stress fibers and forming mounds at high density. They gave positive immunofluorescence for alpha-actin and desmin and their growth was inhibited by heparin at a concentration of 10 ug/ml. All these are characteristic of smooth-muscle-like cells in culture. Their response to specific growth factors was measured by ^{3}H-thymidine uptake after 4 days growth arrest in 0.5% FBS. Both cell types exhibited a clear dose-response to PDGF, with the highest concentration giving values close to maximum (10%FBS). Conversely, the response to bFGF was minimal. Differences in response between the two cell types were seen with IGF-1 (at 0.1-10 ng/ml), while EGF, in the same range, stimulated SMC but not PC. These results may indicate the basis for different patterns of response to injury in the central and peripheral vasculature of the lung. Supported by NHLBI-HL41811

23.4

EFFECTS OF PLATELET ACTIVATING FACTOR ON PULMONARY PHAGOCYTES J.H. Kang,* K. Van Dyke,* W.H. Pailes* and V. Castranova. Div. of Resp. Dis. Studies, NIOSH and West Virginia University, Morgantown, WV 26505

Recruitment and activation of phagocytic cells after inhalation of occupational dusts has been implicated in the development of pulmonary inflammation, fibrosis, or emphysema. Platelet activating factor (PAF) has been described recently as a potent inflammatory agent. The objective of the present study was to investigate if PAF might play a role in the inflammatory response of the lung to occupational dusts. In vitro exposure of alveolar macrophages (AM) to cotton dust (4 mg/ml), silica (10 mg/ml), or coal dust (10 mg/ml) results in the release of nanomolar levels of PAF with a potency of cotton dust > silica > coal dust. In vitro, PAF is a direct stimulant of polymorphonuclear leukocytes (PMN) increasing chemiluminescence (CL) as much as 5-fold over the range of 10^{-10} to 10^{-7}M PAF. In addition, PAF potentiates the response of PMN to a second stimulant, i.e., CL generated from PMN exposed to PAF (10^{-9}M) plus chemotactic peptide (FMLP, 10^{-9}M) is 57% greater than the sum of the separate effects of these stimulants. In contrast, PAF is not a direct stimulant of AM in vitro having no stimulator effect on CL or superoxide release even at levels of 10^{-6} to 10^{-5}M PAF. However, PAF (10^{-5}M) does potentiate zymosan-stimulated activation of CL and superoxide release from AM by 103% and 30%, respectively. These data suggest that the role of PAF in the development of lung disease warrants investigation.

23.5

DETECTION OF CALCIUM IN PULMONARY MACROPHAGES USING ELECTRON SPECTROSCOPIC IMAGING AND ANALYSIS OF ELECTRON ENERGY LOSS SPECTRA. R.C. Stearns and J.J. Godleski. Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115

Intracellular calcium is an important second messenger in many functions of lung macrophages. The purpose of this study is to detect and localize calcium in macrophage organelles ultrastructurally. The Zeiss CEM902, energy filtering electron microscope, can be used to image the structure of unstained, 30 nm sections of cells, to image the distribution of selected elements in such sections, and to determine electron energy loss spectra (EELS) by which elements are identified with absolute specificity and high sensitivity. To study the distribution of elements, preparative techniques must minimize loss of ions during fixation and processing. We have used the Life Cell^{R} CF100 Freeze-slam unit for cryofixation followed by the Life Cell^{R} molecular distillation process and sectioning at 30 nm. To assure our capability to detect calcium, we embedded microprecipitates of $CaPO_4$ in araldite and sectioned the blocks at 30 nm. Calcium was detected in the precipitates by EELS analysis and its distribution was imaged. In macrophages, calcium was detected in the plasma membrane, endoplasmic reticulum, mitochondrial membranes, and to a lesser extent in mitochondrial matrix. The capacity to map the distribution of calcium in macrophages subjected to stimuli will provide important ultrastructural correlations for physiologic studies. (Supported by ES00002, HL27244.)

23.6

PULMONARY CAPILLARY RED BLOOD CELL TRANSIT TIME DURING EXERCISE IN HIGHLY-TRAINED CYCLISTS. G.L. Warren*, K.J. Cureton* and W.F. Middendorf* (SPON: R.B. Armstrong). University of Georgia, Athens, GA 30602

The purpose of this study was to determine if diffusion limitation (i.e., an insufficient time available for equilibration in the pulmonary capillary) could account for the rise in A-aDO2 at high $\dot{V}O2$ ($\geq$ 3.5 l/min). Six highly-trained males (mean $\dot{V}O2max$ = 4.72 l/min) cycled for 4 min at work rates of 55, 65, 75, 85, and 95% of $\dot{V}O2max$. Cardiac output ($\dot{Q}$) was determined using continuous wave Doppler and parasternal 2-D echocardiography. Pulmonary capillary blood volume (Vc) was determined from measurements of single-breath DLCO at two oxygen tensions. Mean red blood cell transit time through the pulmonary capillary bed was calculated by dividing Vc by $\dot{Q}$.

Work Rate	PaO2 (torr)	A-aDO2 (torr)	$\dot{Q}$ (l/min)	Vc (ml)	Transit Time (sec)
Rest	102.6	4.2	5.8	108	1.23
55% $\dot{V}O2max$	94.4	4.3	19.2	144	0.49
65% $\dot{V}O2max$	92.0	7.1	21.8	165	0.45
75% $\dot{V}O2max$	91.0	9.6	25.2	179	0.44
85% $\dot{V}O2max$	89.4	15.0	27.7	191	0.41
95% $\dot{V}O2max$	89.9	18.9	29.6	218	0.45

These results suggest that the rise in A-aDO2 with increasing work rate is not due to a reduction in transit time.

23.7

DIFFERENT EFFECTS OF HYPOXEMIA ON TRACHEAL MUCOSAL AND BRONCHIAL ARTERIAL BLOOD FLOW. S. Elsasser*, W.M. Long, H. Baier, R. Abello*, A. Chediak and A. Wanner. Pulmonary Division, VAMC, University of Miami at Mount Sinai Medical Center, Miami Beach, FL 33140.

Airway mucosal and bronchial arterial perfusion may be regulated by different factors. We determined the effects of hypoxemia on tracheal mucosal ($\dot{Q}_{tr}$) and bronchial ($\dot{Q}_{br}$) blood flow measured with an inert soluble gas technique and an electromagnetic flow probe, respectively. In seven lightly anesthetized sheep, 20 minutes of hypoxemia (PaO_2 42.0+6.1 Torr [mean + SD]) decreased $\dot{Q}_{tr}$ from 1.2 $\pm$ 0.4 to 0.9 $\pm$ 0.4 ml/min ($p < 0.05$). In another six sheep, hypoxemia (PaO_2 34.7+ 8.8 Torr [mean + SD]) maximally increased $\dot{Q}_{br}$ from 11.1 $\pm$ 3.7 to 18.8 $\pm$ 9.5 ml/min ($p < 0.05$), however after 45 minutes of hypoxemia $\dot{Q}_{br}$ declined to near its baseline value. The rise in $\dot{Q}_{br}$ correlated with cardiac output ($r = 0.48$; $p < 0.05$), but not with mean arterial pressure. We conclude that 1) arterial hypoxemia decreases $\dot{Q}_{tr}$ and increases $\dot{Q}_{br}$, 2) hypoxia induced increases in $\dot{Q}_{br}$ may be in part related to augmented cardiac output, 3) hypoxic alteration of airway mucosal and bronchial perfusion may occur via different mechanisms. (Supported by NIH grant HL-34668, Veterans Administration and Stiftung fur Pneumologie, Switzerland).

23.8

PULSATILE PRESSURE TRANSMISSION IN THE CANINE PULMONARY VASCULAR TREE. J.M. Maarek, Y.T. Zhang, and H.K. Chang, Department of Biomedical Engineering, University of Southern California, Los Angeles, CA 90089-1451.

The arterial pressure tracing following a rapid occlusion of the pulmonary artery enables one to obtain the pressure at the distal end of the pulmonary arterial tree (Pao). We hypothesized that Pao reflects the oscillations of the pulmonary artery pressure (Ppa) as they are transmitted through the vascular tree. In 7 isolated left lower lobes of canine lung perfused by a pulsatile flow pump, set at 0.6, 0.9, 1.2, and 1.5 Hz and a constant mean flow of 0.4 l/min, we performed rapid occlusion of the lobar artery at 16 instants, equally distributed within a pump cycle. From the 16 determinations obtained for each frequency, Pao pressure waves were reconstructed, exhibiting a phase lag with respect to the corresponding Ppa waves. As the pump frequency decreased from 1.5 Hz to 0.6 Hz, the amplitude of the Ppa waves increased from 12.8mm Hg to 15.5mm Hg and the peak-to-peak oscillation of the Pao waves increased from 1.5mm Hg (11% of the Ppa waves) up to 3.8mm Hg (24% of the Ppa waves); correspondingly, the ratio of the first harmonic of the Pao wave over that of the Ppa wave increased from 0.18 to 0.30. Furthermore, the phase lag between these two harmonics increased from 47 degrees up to 82 degrees. We conclude that the pulmonary arterial tree behaves as a low-pass filter and that its transmission properties can be studied with the aid of the arterial occlusion technique. (Supported by NHLBI Grant HL36908).

23.9

CHRONIC HYPOXIC EXPOSURE PREVENTS THE INCREASE IN PUMONARY VASCULAR REACTIVITY TO ACUTE HYPOXIA (BUT NOT ANGIOTENSIN II) INDUCED BY MONOCROTALINE. E. Kenneth Weir, Daniel P. Nelson* and Stephen L.Archer VA Medical Center, Minneapolis, MN 55417

The interaction of chronic hypoxia (CH) and monocrotaline (MC) in causing pulmonary hypertension and in altering pulmonary reactivity was studied in 4 groups of rats: normoxic controls (NC) n=10; MC, n=8; CH, n=12; and CH+MC, n=13. Pulmonary arterial pressure and resistance measured in vivo, as well as right ventricular hypertrophy, were greatest in the CH+MC group. Pulmonary vascular reactivity to acute hypoxia and angiotensin II (A II) was assessed in isolated lungs perfused with Krebs-albumin.

Perfusion Pressure mmHg	Normoxia	Acute Hypoxia	A II
NC	7±0.4	2±0.5	1±0.1
MC	8±0.2	19±1.9	12±2.4
CH	9±0.3	0.3±0.2	2±0.4
CH+MC	13±0.5*	0.6±0.2*	11±1.5

* CH+MC different from MC alone: $p<0.05$. Mean and SEM.

The increased reactivity to acute hypoxia seen in MC lungs was ablated by exposure to chronic hypoxia but the increased reactivity to angiotensin II was preserved. This marked disparity in reactivity to acute hypoxia and angiotensin II may provide a model for studies of the mechanism of acute hypoxic vasconstriction. (Supported by VA Merit Review Grant)

23.10

NEURONAL TYPE N CALCIUM CHANNELS MEDIATE NOREPINEPHRINE RELEASE IN RABBIT PULMONARY ARTERY. James A. Russell, E.C. Giese* and T.L. Moore*, SUNY at Buffalo, Buffalo, NY 14214.

Voltage sensitive calcium channels (VSCC) including type N and Ln are present in neurons and they differ from Lm VSCC on smooth muscle cells. Omega conotoxin blocks N and Ln channels but not Lm channels. Verapamil blocks Ln and Lm but not N channels. This study was designed to determine whether N or Ln channels mediate norepinephrine (NE) release in isolated rings of rabbit pulmonary artery. The release of endogenous NE from intramural sympathetic neurons was obtained through field electrical stimulation (ES) of the tissues. Conotoxin (10^{-6}M) had no effect on pulmonary artery contractions induced by 40mM K^+ or NE (10^{-9}-10^{-5}M) but significantly depressed the response to ES (21V, 0.5msec pulse duration) at all stimulus frequencies (1-20Hz). Verapamil ($5x10^{-6}$M) significantly depressed 40mM K^+-induced contractions by 86±2% as well as contractions induced by ES (1-20Hz) and NE (10^{-9}-10^{-5}M). Moreover, for contractions of equal magnitude, verapamil depressed the response to ES and NE to the same degree. We conclude that type N calcium channels mediate NE release in rabbit pulmonary artery.

23.11

TONE-DEPENDENT EFFECTS OF ALMITRINE ON HYPOXIC PULMONARY VASOCONSTRICTION IN DOGS. R. Naeije, P. Lejeune*, C Mélot*, M. Leeman*, S. Brimioulle*, J.L. Vachiéry*. Respiratory Research Unit, Erasmus Hospital, Brussels, Belgium.

Almitrine is a peripheral chemoreceptor stimulant that has been reported either to enhance or to inhibit hypoxic pulmonary vasoconstriction (HPV) by a direct effect at the pulmonary vessels. We investigated the effects of low i.v. doses of almitrine on pulmonary arterial pressure (Ppa) - cardiac output (Q) plots in 32 pentobarbital-anesthetized dogs ventilated in hyperoxia (FIO_2 0.4) or in hypoxia (FIO_2 0.1). Q was manipulated by inflation of a balloon in the inferior vena cava. HPV, defined as a hypoxia-induced increase in Ppa over the entire range of Q studied, from 2 to 5 l/min, was elicited 16 dogs. In these "responders" almitrine 4 μg/kg/min (n=8) increased Ppa at all levels of Q at FIO_2 0.4 and decreased Ppa at all levels of Q at FIO_2 0.1, so that HPV was inhibited, and almitrine 2 μg/kg/min (n=8) had no vascular effect. In the other 16 dogs, hypoxia did not affect Ppa over the entire range of Q. In these "nonresponders" almitrine 4 μg/kg/min (n=8) as well as 2 μg/kg/min (n=8) increased Ppa at all levels of Q more at FIO_2 0.1 than at FIO_2 0.4, so that HPV was restored. We conclude that the pulmonary vascular effects of almitrine appear to be dependent not only on the dose but also on the preexisting pulmonary vasoreactivity to hypoxia. This may explain previously reported discrepant effects of almitrine on HPV.

23.12

INFLUENCE OF CARDIAC OUTPUT ON GAS EXCHANGE IN DOGS WITH NORMAL AND ACUTELY HYPOXIC LUNGS. C.Mélot*, P. Lejeune*, M. Delcroix*, M. Leeman*, R. Naeije. Laboratory of Cardio-Respiratory Physiology, Erasmus Hospital, Brussels, Belgium.

We investigated the effects of changes in cardiac output (Q) on pulmonary arterial pressure (Ppa) and on gas exchange as assessed by the multiple inert gas elimination technique in 26 pentobarbital-anesthetized dogs ventilated in hyperoxia (FIO_2 0.4), and after either hypoxic ventilation with a FIO_2 of 0.1 (n=19) or injection of 0.09 ml/kg oleic acid (n=7). Q was manipulated by inflation of a balloon in the inferior vena cava. Hypoxia as well as oleic acid increased Ppa at all levels of Q studied, from 1 to 5 l/min. VA/Q distributions were measured at the highest and at the lowest Q. In hyperoxia, decreasing Q shifted the VA/Q distributions towards a higher VA/Q without change in the dispersions of VA and of Q distributions. Hypoxia shifted VA/Q distributions towards a higher VA/Q without a change in the dispersions of VA and of Q distributions. Oleic acid increased true shunt (Qs/Qt) and the dispersion of Q distributions. Decreasing Q after oleic acid decreased Qs/Qt and shifted the VA/Q distributions towards a higher VA/Q, still without change in the dispersion of VA or in Q distributions. We conclude that in normal or in diffusely abnormal canine lungs, a decrease in Q, like hypoxic pulmonary vasoconstriction, improves gas exchange by a shift of VA/Q distributions towards a higher VA/Q, and by a decrease in Qs/Qt when abnormally high.

23.13

COMPARATIVE ACCUMULATION OF LIDOCAINE (LIDO) AND SUFENTANIL (SUF) IN THE ISOLATED PERFUSED RABBIT LUNG (IPL) D.L. Roerig, S.B. Ahlf, C.A. Dawson, J.H. Linehan, J.P. Kampine. Depts.. of Anesthesiology, Pharmacology/Toxicology and Physiology. Med. College of WI. and VA Med. Ctr., Mil.WI. 53295

Previously we reported first pass uptakes in the human lung for lido and suf of 60.4% and 60.2% respectively (FASEB J. 2:A951, 1988, Pharmacologist 30:A93, 1988). The similarity between the uptake of these basic lipophilic amines in the human lung was surprising because suf has a higher pka and is 33 times more lipid soluble than lido. In the human studies information about the overall time course of accumulation is limited by recirculation. Therefore, pulmonary accumulation of suf and lido was further examined in the rabbit IPL by multiple indicator dilution. The IPL was perfused with Krebs-Ringer bicarbonate buffer containing 4.5% bovine serum albumin (BSA) or a non-protein colloid. After bolus injection, venous outflow was sampled for 20 min. In the presence of BSA, first pass uptakes of lido and suf (53.2±1.7% and 62.0±1.2% respectively) were similar to those observed in the human lung. However, if first pass uptake and diffusion back out of the lung were expressed as a mean transit time($\bar{T}$), drug-lung tissue interactions for these drugs were very different. $\bar{T}$ for lido was 10.4±.6 sec compared to 55.6±.8 sec ($P<0.05$) for suf indicating a longer tissue residence time for the more lipophilic suf. In the absence of BSA,$\bar{T}$ for lido and suf increased to 29.0±.9 sec and 267±27 sec respectively. Therefore, plasma protein binding is a factor in pulmonary drug uptake and the large effect on $\bar{T}$ for suf is consistant with its greater binding in plasma. In the absence of BSA, the large difference in $\bar{T}$ between lido and suf is more consistant with their physicochemical properties.

23.14

INFLUENCE OF LUNG INJURY ON EFFECTIVE OUTFLOW PRESSURE OF THE PULMONARY CIRCULATION. M. Leeman*, P. Lejeune*, J. Closset*, J.L. Vachiéry*, S. Brimioulle*, C. Mélot*, R. Naeije. Laboratory of Cardio-Respiratory Physiology, Erasme Hospital, Brussels, Belgium.

To test for an increase in closing pressure in canine oleic acid (OA) lung injury, we studied (1) the pulmonary artery pressure (Ppa) : cardiac index (Q) relationship with left atrial pressure (Pla) kept constant (n = 7) and (2) the Ppa : Pla relationship with Q kept constant (n = 9) in intact anesthetized and ventilated dogs before and after lung injury induced by OA 0.09 ml/kg iv. Q was manipulated using a femoral arteriovenous bypass and a balloon catheter inserted in the inferior vena cava. Pla was manipulated using a balloon catheter placed by thoracotomy in the left atrium. Ppa:Q plots were linear before and after OA. Before OA, the extrapolated pressure intercept of the Ppa:Q plots approximated Pla. OA administration resulted in a parallel shift of the Ppa:Q plots to higher pressures, i.e. the pressure intercept increased while the slope was unchanged. Increasing Pla at constant Q before OA led to a proportionnal augmentation of Ppa. After OA, however, changes in Pla over the same range affected Ppa only at the highest levels of Pla. These data suggest that Pla is the effective outflow pressure of the pulmonary circulation in intact anesthetized dogs. In lung injury, the closing pressure of the pulmonary vessels increases, exceeds Pla, becomes the effective outflow pressure and is responsible for the pulmonary hypertension.

23.15

CLEARANCE OF ^{99m}Tc-DTPA FROM THE SHEEP TRACHEAL LUMEN. J.G.Widdicombe, Z.Hanafi*, D.R.Corfield* and S.E.Webber*, Dept of Physiology, St George's Hosp Med School, London SW17 0RE, UK.

8 sheep were anaesthetized (pentobarbitone, 20mg.kg^{-1}), paralysed (gallamine, 1mg.kg^{-1}) and artificially ventilated. Tracheal arteries were perfused with blood at constant flow and perfusion pressures measured. A vein from the tracheal segment was cannulated and its blood collected. The perfused trachea was filled with Krebs-Henseleit solution containing ^{99m}Tc-diethylene-triamine-penta-acetate (DTPA). Tracheal clearance of DTPA was determined from venous blood DTPA. The effects (% change from control, *p<0.05) of changing perfusion flow rate and of changing perfusion pressures by intra-arterial drugs were (means ± s.e.m.s):

	n	P, perfusion	Q, vein	Output, DTPA
Pump flow -50%	5	-33 ± 3*	-10 ± 4	+46 ± 34
Change -100%	10	-80 ± 8*	-24 ± 8*	+182 ± 67*
+50%	7	+36 ± 3*	+12 ± 3*	-28 ± 7*
Methacholine	4	-27 ± 5*	+5 ± 2	+20 ± 21
Phenylephrine	4	+17 ± 8	+19 ± 17	+11 ± 28

Thus a decrease in perfusion decreases perfusion pressure and venous outflow but increases DTPA output. An increase in perfusion does the opposite. Changing perfusion pressure with drugs, with blood flow constant, alters venous outflow without significant changes in DTPA output. The mechanisms underlying these results are yet to be established but may involve interstitial fluid volume.

23.16

FUNCTIONAL HETEROGENEITY OF PULMONARY ARTERIAL SMOOTH MUSCLE. Betty M. Twarog, Graham LeM. Campbell*, Steven Petrou*, Inger Wahlqvist* and Robert M. Marcus*. Graduate Hospital, Philadelphia, PA 19146.

This study was designed to delineate heterogeneity of responses to agonists in vessel segments from defined loci of the rat pulmonary arterial bed; to provide the physiologic data for correlative studies of phenotype organization of cytoskeletal proteins; and a baseline for sequential studies of hypertrophying pulmonary artery segments isolated from rats in which pulmonary hypertension has been induced by exposure to chronic alveolar hypoxia.

Contractility and responsiveness to agonists of smooth muscle cells were observed in vessel segments from the rat pulmonary arterial bed. In normoxic rats ranging from 6 to 18 weeks of age, active tension in response to high K^+, norepinephrine (NE) and serotonin (5-HT) was measured in extrapulmonary elastic arteries, the proximal and distal segments of the main (common) pulmonary trunk (P-MPA, D-MPA), the right and left pulmonary arteries (LL') and a small muscular intrapulmonary artery (SPA). Active stress was calculated. Tension, stress and percent maximum response were plotted against concentration. Among the extrapulmonary elastic arteries, maximum active tension and stress in response to high K^+ were greatest in P-MPA and least in LL'. The SPA generated less tension than the larger vessels, but stress generation was similar to that in P-MPA. In all segments, the maximum active stress in response to agonists was less than to K^+. SPA contracted weakly in response to NE and at a concentration of 5 x 10^{-7} M, beta-receptor activated relaxation was evident. Relative responsiveness to K^+ and agonists showed minor differences: D-MPA was more sensitive than P-MPA to NE but less sensitive to 5-HT. A major difference was the pronounced diminution of the beta response to NE in the SPA as the rats aged. The results indicate functional heterogeneity among smooth muscle cell populations, not only in small muscular vessels compared to elastic vessels, but in adjacent segments of elastic arteries. (Supported by HL34214.)

23.17

RESPONSES OF ISOLATED, CANNULATED FELINE PULMONARY ARTERIES TO PRESSURE. Jane A. Madden, V.A. Medical Center & The Medical College of Wisconsin, Milwaukee, WI 53295.

Isolated pulmonary arteries from the cat regularly develop spontaneous tone in response to stretch and exhibit oscillatory behavior under certain conditions. Now we have found that, when cannulated and pressurized, these arteries can develop vasomotor tone in response to increasing pressure. This behavior was unexpected since in the absence of hypoxic vasoconstriction, the pulmonary circulation is a low resistance vasculature in which changes in pulmonary blood flow are, to a large extent, passively accommodated. These data suggested that isolated small pulmonary arteries may possess characteristics in common with resistance arteries from other vascular beds. Arteries (200-400μm diameter) were dissected from cat lungs and approximately 8 mm long segments were mounted on glass cannulas in a chamber containing warmed, oxygenated physiological saline solution (PSS). All side branches were tied off and the vessel stretched to its approximate resting length *in situ*. Internal pressure was adjusted by raising or lowering a reservoir filled with the same PSS. The vessels were observed and their diameter measured with a video system. During a 90 minute equilibration at 10 mm Hg the vessels developed spontaneous tone with diameters decreasing a maximum of 44% and eventually stabilizing at 27% of initial diameter. Pressure was increased in 5 mm Hg steps from 5 to 30 mm Hg and reduced in the same fashion. Diameters were measured at the moment of the pressure change and at 1,2, and 3 minutes thereafter. Raising pressure from 5 to 10 mm Hg resulted in an increase in vessel diameter. From 10-30 mmHg the diameter changed substantially less. At all pressures diameter decreased during the 3 minutes. These data indicate that feline pulmonary arteries may possess some vasomotor capabilities since they constrict in response to an immediate increase in pressure and above 10 mm Hg they show relatively small diameter changes. *Support: VA Med Res Funds.*

23.18

EFFECT OF EXTERNAL Na^+ ON RESTING TENSION IN RAT PULMONARY AND MESENTERIC MUSCULAR ARTERIES. Mary L. Tod, Xiaojian Yuan*, Lewis J. Rubin and Mordecai P. Blaustein. Univ. of Maryland School of Medicine, Baltimore, MD 21201.

The transmembrane Na^+ gradient plays an important role in the regulation of intracellular Ca^{2+} in vascular smooth muscle. In 6 experiments, unstimulated (resting) tension was compared before and after K^+-induced contractions in rings (< 0.5 mm, O.D.) of rat muscular pulmonary (PA) and mesenteric arteries (MA) during normoxia (Po_2 = 125 ± 6 torr, mean ± SEM) and hypoxia (Po_2 = 31 ± 3 torr). When $[Na^+]_o$ was reduced from 139.2 to 1.2 mM by replacing NaCl with N-methylglucamine, during normoxia the resting tension was unaltered before K^+-induced contractions. However, following K^+-induced contractions, the resting tension was increased significantly above baseline in PA (92 ± 17%, $p < 0.01$), but only slightly in MA (14 ± 8%, NS). PA and MA tension returned to the original baseline when normal $[Na^+]_o$ was restored. During low $[Na^+]_o$, hypoxia increased resting tension in PA by 110 ± 17% ($p < 0.01$), but not in MA (17 ± 9%, NS). After K^+-induced contractions, resting tension remained significantly elevated in PA (122 ± 15%, $p < 0.01$), but was only slightly increased in MA (22 ± 12%, NS). Furthermore, return to normoxic conditions did not restore tension to baseline in PA or MA until normal $[Na^+]_o$ was replaced. We conclude that $[Na^+]_o$ influences resting tension of both PA and MA, presumably via a Na^+/Ca^{2+} exchange; this mechanism appears to have a greater effect in pulmonary than in mesenteric arteries.

23.19

EFFECT OF VENTILATION ON PULMONARY ARTERIAL ELASTICITY. Brydon J.B. Grant, Cheng-Lung Lee* and Baruch B. Lieber*, Depts. of Medicine and of Mechanical & Aerospace Engineering, SUNY, Buffalo, NY 14215

Previously (FASEB J. 3:A380, 1989), we reported that pulmonary arterial compliance (C_a) increased with inspiration, but not with positive end expiratory pressure (PEEP). This suggests that C_a is time varying. In the present study, we calculated pulmonary arterial elasticity (E_{pa}) from pressure (P) and diameter (D) of the main pulmonary artery in 7 open-chest dogs under chloralose anesthesia. P and D were measured with a micromanometer tipped catheter and sonomicrometry respectively, at 3 levels of PEEP. dP/dD was calculated by Fourier analysis from the ratio of the amplitude of pressure to diameter oscillations at ventilatory frequency (0.2 Hz) and at cardiac frequency (~3 Hz). At 3 Hz, there was no significant difference between dP/dD at the start of inspiration (I) and dP/dD at the start of expiration (E). This suggests E_{pa} is not time-varying. dP/dD was significantly higher at 0.2 Hz than 3 Hz, indicating E_{pa} is frequency dependent. The measurements of mean PAP and mean D at each level of PEEP were used to determine the pressure-diameter relation under quasistatic conditions. dP/dD was 325 cm $H_2O.cm^{-1}$ at I and 183 cm $H_2O.cm^{-1}$ at E. Previously, we found that the reduction of pulmonary arterial flow with PEEP was greater during E than I. Therefore, the decrease of dP/dD between I and E may be related to a reduction of flow mediated vasodilatation during inspiration.

23.20

SEGMENTAL CONTRACTILE RESPONSES TO BRADYKININ IN THE ISOLATED GUINEA PIG PULMONARY ARTERY. Ricardo Saban* and Dale E. Bjorling*. (Spon: G.E. Bisgard). School of Vet. Medicine, Univ. of Wisconsin- Madison, WI. 53706

Bradykinin (BK) is known to release EDRF from bovine pulmonary arteries and veins and porcine coronary arteries. It also activates phospholipase A2 releasing arachidonic acid from vascular endothelial cells and stimulates PGI2 formation in bovine aortic endothelial cells. We examined the effects of BK on the proximal half of the guinea pig main pulmonary artery (PM) and the extralobar left main branch of the pulmonary artery (LB), both suspended as rings in isolated tissue baths. The presence of endothelial cells was determined at the end of each experiment by the addition of acetylcholine (10-5 M). Cumulative dose-response effects were expressed as a percentage of the maximum contraction produced by barium chloride. BK induced a dose-related contraction in both segments with maximum responses of 65% for LB and 25% for the PM. EC50 values were about the same for both segments (2X10-7M). Indomethacin 5X10-6 M reduced the maximum response in LB without altering the responses of the PM. The responses were not abolished by the removal of the endothelium or by the pretreatment of the animals with reserpine (5 mg/kg,i.p., 10-16 hours beforehand). When the tissues were precontracted with phenylephrine (2X10-6M), BK induced a biphasic response in the PM: a relaxation in response to 10-9 M to 10-8 M and contraction at higher concentrations (3X10-8 to 3x10-6M). The precontracted LB contracted in response to BK. The data suggest a differential response to BK dependent on the particular segment studied. Contraction of the pulmonary artery in response to BK suggests a possible role of this peptide in pulmonary hypertension. (Support by Grant SVM 101-0678).

23.21

DIVERGENT RESPONSES OF SMALL PULMONARY AND MESENTERIC MUSCULAR ARTERIES TO K^+ AND HYPOXIA. Xiaojian Yuan*, Mary L. Tod, Lewis J. Rubin and Mordecai P. Blaustein. Univ. of Maryland Med. Sch., Baltimore, Md, 21201 USA

Tension was compared in unstimulated (resting) and K^+-depolarized rings ($\leq$ 0.5 mm o.d.) of rat small muscular pulmonary (PA) and mesenteric (MA) arteries during normoxia (Po_2 = 117 torr) and hypoxia (Po_2 = 22-43 torr). During 100-120 min of hypoxia, resting PA tension increased gradually from 1380 $\pm$ 101 mg/mg wet wt (ww) to 2142 $\pm$ 128 mg/mg ww, $p < 0.01$, n = 20, while resting MA tension did not change (1122 $\pm$ 56 to 1071 $\pm$ 62 mg/mg ww, N.S., n = 9). The increase in resting PA tension was external Ca^{2+}-dependent. Return to normoxia for 1 hr led to partial recovery in PA (to 1546 $\pm$ 79 mg/mg ww, $p < 0.01$), while MA resting tension declined slightly (to 982 $\pm$ 75 mg/mg ww, N.S.). The $[K^+]_o$ that induced 50% of the 100 mM K^+-evoked tension (ΔT_{100K}) was ~36 mM in MA, and only ~13 mM in PA during normoxia; PA tension reached a plateau at $[K^+]_o \geq$ 20 mM, whereas the $[K^+]_o$-versus-tension curve for MA did not reach a plateau at $[K^+]_o$ = 100 mM. During hypoxia, the $[K^+]_o$-tension curves for both PA and MA were suppressed (ΔT_{100K} for PA declined from 2538 $\pm$ 371 to 1719 $\pm$ 242 mg/mg ww and ΔT_{100K} for MA declined from 5273 $\pm$ 536 to 3554 $\pm$ 415 mg/mg ww), but the curves were not shifted along the $[K^+]_o$ axis. The $[K^+]_o$-tension curves in both PA and MA returned toward the controls upon restoration of normoxia. These data show that hypoxia induces reversible resting vasoconstriction in isolated rat muscular PA but not MA, and attenuates vasoconstriction in response to elevated $[K^+]_o$ in both PA and MA.

23.22

EFFECT OF FPL 55712 ON GAS EXCHANGE DURING HYPOXIA IN THE METHACHOLINE (MCH)-CHALLENGED MONGREL DOG. Walter Schaffartzik, Jose Arcos*, Koichi Tsukimoto* and Peter D. Wagner. Dept. of Med., Univ. of Calif. San Diego, La Jolla, CA 92093

We previously reported that when air breathing mongrel dogs were challenged with MCH, gas exchange was unaffected by prior leukotriene blockade by FPL 55712 (ARRD 139:A586, 1989). In contrast, in the antigen-challenged Basenji-Greyhound, the same 25 mg inhaled dose of FPL greatly worsened gas exchange due to increased $\dot{V}_A/\dot{Q}$ mismatching (Boynton et al., J. Crit. Care 2(1):27-35, 1987). To further explore the role of leukotrienes in (experimental) asthma, we repeated these studies in 8 mongrel dogs, each challenged with MCH twice: once breathing 100%, and again breathing 13% O_2 (in random order). Without FPL, a standard dose of MCH (1% inhaled at 15 breaths/min for 90 sec) produced significantly less $\dot{V}_A/\dot{Q}$ mismatch in hypoxia than in hyperoxia. However, FPL 55712 pre-treatment increased the amount of mismatch after MCH in hypoxia to the level seen in hyperoxia. These data thus show substantial effects of FPL 55712 worsening gas exchange in MCH-challenged dogs breathing hypoxic but not hyperoxic gas. There were no effects of FPL on airways resistance or lung volume, and we suggest that FPL may be interfering with hypoxic pulmonary vasoconstriction. While it remains important to similarly examine other leukotriene end-organ antagonists, the present data suggest that leukotrienes released by the interaction between MCH and hypoxia may be important vasoconstrictor regulators of the pulmonary circulation. (Supp. by HL 1773.)

CONTROL OF BREATHING

24.1

REFLEX VENTILATORY EFFECTS OF KCL STIMULATION OF LUNG RECEPTORS WITH NON-VAGAL AFFERENTS. R.L.Coon, P.S. Clifford, F.A. Hopp, and E.J. Zuperku. Med. College of WI. and VA Med. Ctr., Mil.WI. 53295

A number of studies have shown that lung receptors with non-vagal afferents do exist. The purpose of this study was to determine the reflex ventilatory effects produced by increased non-vagal afferent nerve activity from the lungs. Five dogs were anesthetized with sodium pentobarbital and placed on positive pressure ventilation. The chest was opened through a sternal split. Diaphragm EMG and EMGs from the right and left triangularis sterni (TS-EMG) were recorded along with systemic arterial blood pressure and tracheal pressure. Post-vagotomy, measurements of these parameters were made before and after a KCl solution was applied with a cotton swab to the right or left lung near the venous hilum. KCl applied to the lung near the left venous hilum increased left TS-EMG 68% and, similarly, applied to the right lung, reflexly increased right TS-EMG 28%. TS-EMG on the contralateral side either decreased or remained unchanged. Breathing frequency and peak diaphragm EMG were not significantly affected. (Supported by The Medical Research Service of the VA)

24.2

RAPID COMPONENT IN LARYNGEAL APERTURE RESPONSE TO EXPIRATORY RESISTANCE LOADING IN HUMANS REVEALED USING VIDEO IMAGE ANALYSIS. Robert W. Giering* and J. Andrew Daubenspeck. Dartmouth Medical School, Hanover, NH 03756.

We have previously shown that the laryngeal aperture narrows more during resistance loaded than during control expirations (Daubenspeck and Bartlett, Resp. Physiol. 54:307, 1983). We wanted to determine whether the aperture response was linked temporally to the alteration in the volume time course resulting from the load application or whether receptors in the upper airway responsive to transmural airway pressure might initiate an earlier response. Video frames at 0.1 sec intervals were analyzed to determine the time course of the aperture response to an expiratory resistance load of 5 cm H2O/LPS. Images of the larynx obtained from 3 subjects during control and loaded expirations were analyzed. We measured expired volume to get comparisons between the changes in lung volume and glottal area under control and loaded conditions. In 2 subjects, the earliest significant (sig.) decrease in area occurred c. 10% into expiratory duration (TE), whereas the earliest sig. deviation of lung volume from the control trajectory did not occur until about 20% into TE. The third subject showed a sig. aperture change after 15% TE while the volume change became sig. after 25% TE. Thus aperture control in this situation may be influenced by pressure detection and feedback. Mechanoreceptors in the upper airway are the most likely source of this feedback. (Supported by NHLBI grant HL29068.)

24.3

RESPIRATORY MUSCLE AND AIRFLOW TIMING IN LAMBS. A.A. Hutchison*, J.W. Wozniak*, H.G. Choi*, M. Conlon*, R.A. Otto*, C.A. Hammond*, P.C. Kosch & R.M. Abrams. Univ. of Florida, Depts. of Pediatrics, Physiol. Sci., Biostatistics, Otolaryngol. & Ob./Gyn., Gainesville, Fl. 32610.

Timing relationships between inspiratory (VI) and expiratory (VE) airflow, posterior cricoarytenoid (PCA), thyroarytenoid (TA) and diaphragmatic (DEMG) activities were studied. Data, recorded after C-section birth in 5 previously instrumented lambs, were digitized for computer analysis of an early respiratory pattern (A) [199 breaths] and a later one (B) [189 breaths]. Early VE in A was braked for 0.55+/-0.05 (mean+/-SD) of expiration. Within PCA activity in A, two bursts occurred: PCA1 in late expiration and PCA2 with inspiration. The onsets of PCA1 and PCA2 to VI onset times were 227+/-18 milliseconds (msec) and 121+/-12 msec, the latter exceeding the onset PCA-VI time in B - 101+/-15 msec [$p<0.001$]. The DEMG and VI onset intervals were 123+/-28 msec (A) v. 102+/-18 msec (B) [$p<0.001$]. Return to baseline (B/L) DEMG activity to onset VE was less in A (35+/-12 msec) than B (89+/-29 msec) [$p<0.001$]. TA activity was present in A, the time from TA onset to VE onset being 81+/-33 msec. In A, the times from 1) return to B/L PCA inspiratory activity, 2) onset of TA and 3) the first TA plateau value to braked VE onset were 1) 87+/-14 msec, 2) 116+/-37 msec and 3) 53+/-33 msec. The times from 1) return to B/L TA activity and 2) onset of PCA1 to late VE increase were 1) 28+/-48 msec and 2) -7+/-15 msec. Close timing relationships suggest active laryngeal control of airflow pattern in newborn lambs. (Supported by NIH grant HL 39858)

24.4

DOES BODY POSITION ALTER THE VENTILATORY RESPONSES OF CYSTIC FIBROSIS PATIENTS (CF) TO EXPIRATORY THRESHOLD LOADS (ETLs)? F. Cerny, L. Armitage*, J. Hirsch, B. Bishop. SUNY/Buff.Buffalo, NY 14214

Minute ventilation (Ve), frequency (F), tidal volume (Vt) and the durations of inspiration (Ti) and expiration (Te), and end-tidal CO_2 (CO_2) were measured in severe CF patients and in healthy subjects (H) during graded ETLs while supine and 60° head-up. At 0 ETL, Ve, Vt, and F were higher in CF than in H in both positions. In CF, Ve was independent of load and position; in H, Ve increased with increases in load and was highest at 60°. In CF, Vt increased on a 5 cm H_2O load but increased no further with higher ETLs. In H, Vt increased with each load in both positions. In CF, F decreased progressively across loads in both positions. In H, F decreased on 5 ETL in both positions but changed no further on higher loads. Ti was independent of load and position, but was shorter in CF than in H. Te increased on 5 ETL in both groups and remained constant across higher loads in both positions. In CF, CO_2 was not dependent on load or position, but in H, CO_2 decreased with each load; decreases were smaller when supine. Unlike those of H, ventilatory responses of CF to ETLs did not change with a change in body position. CF Fdn. Grant G204 9-01.

24.5

ARE VENTILATORY RESPONSES TO EXPIRATORY THRESHOLD LOADS (ETL) NORMAL IN CYSTIC FIBROSIS (CF)? Lisa Armitage*, Frank Cerny, Judith Hirsch and Beverly Bishop. SUNY at Buffalo, Buffalo, NY 14214

Minute ventilations (Ve), tidal volumes (Vt), frequencies (F), the durations of inspiration (Ti), expiration (Te) and end-tidal CO_2 (CO_2) were measured in healthy (H) and CF subjects while expiring against ETLs of 0 to 25 cm H_2O (ETL). With no load, Ve, Vt, and F were higher (with equal reductions in Ti and Te) in CF compared to H. CO_2 was lower in CF than in H. With increasing ETLs, Ve remained unchanged in CF but increased in H. Vt increased in both groups at a 5 cm ETL. During ETLs above 5, Vt continued to increase in H, but not CF. From 0 to 5 cm H_2O, F decreased in CF less than in H; with increasing loads F decreased further in CF but not in H. Ti remained shorter in CF than in H at every load without change across loads in either group; Te increased in both groups across loads. CO_2 did not change during ETLs in CF but decreased in proportion to load in H. Breathing patterns and ventilatory responses to ETLS are abnormal in CF patients. Supported by CF Fdn. Grant G204 9-01.

24.6

EFFECTS OF WATER DEPRIVATION ON VENTILATORY PARAMETERS IN RATS. Graham D. Smith* (SPON: E.H. Schlenker), University of South Dakota, School of Medicine, Vermillion, SD 57069.

The purpose of this study was to examine the effects water (H_2O) deprivation has on ventilatory parameters. Eight male rats (253.6g ± 5.5 mean ± SE) were H_2O deprived for 48 hours and then given free access to H_2O. Parameters were recorded prior to, and during 24 and 48 hours of H_2O deprivation as well as after 24 hours and three days of rehydration. Recordings of body weight and rectal temperature were taken each day prior to determination of ventilatory parameters. Respiratory H_2O loss, tidal volume (Vt), frequency of breathing (f), minute ventilation (V_E), 0_2 consumption, and CO_2 production were determined using a modified plethysmograph. V_E, Vt, and f were also recorded during hypercapnic challenge (7% CO_2). Significant ($P < 0.05$ mean ± SE) decreases were seen after 48 hours of H_2O deprivation in body weights (253.6 ± 5.5 to 208.1 ± 4.1g), rectal temperatures (36.6 ± 0.3 to 35.6 ± 0.2° C), and respiratory H_2O loss ($4.9 \times 10^{-5} \pm 0.9 \times 10^{-5}$ to $1.7 \times 10^{-5} \pm 0.3 \times 10^{5}$ kg H_2O/1 air/kg weight). Other significant changes included a drop in Vt (normal air 0.9 ± 0.1 to 0.5 ± 0.1ml, hypercapnia 1.5 ± 0.2 to 0.7 ± 0.1ml), f during hypercapnic challenge (228.8 ± 1.8 to 187.5 ± 7.5 breaths/minute), CO_2 production (0.7 ± 0.1 to 0.4 ± 0.1 cc/g/hr),and V_E (normal air 125.4 ± 19.1 to 66.8 ± 21.7ml, hypercapnia 355.6 ± 55.1 to 141.81 ± 20.6ml). Upon rehydration all parameters returned to approximately normal levels. The markedly blunted response of V_E to hypercapnia during H_2O deprivation could be of metabolic origin but mechanisms have yet to be elucidated.

24.7

ASPARTIC ACID STIMULATES BOTH METABOLISM AND VENTILATION OF ANESTHETIZED RATS. Evelyn H. Schlenker, U.S.D. School of Medicine, Vermillion, S.D. 57069.

Rats anesthetized with 60 mg/kg sodium pentobarbital and given subcutaneous injection of saline or aspartic acid (100,250, or 580 mg/kg) showed simultaneous increases of both ventilation and carbon dioxide production in a dose dependent manner compared to control rats who only received the anesthetic. Ventilation was increased predominantly by an increase in the frequency of breathing (saline value, 72.6 ± 3.6; 100mg/kg value, 88.9 ± 6.8; 250 mg/kg value, 97.0 ± 6.9; 580mg/kg value 107.3 ± 8.8 breaths per minute). In contrast, rats who only received anesthetic averaged 71.4 breaths per minute over the one hour experimental period. The increased frequency of breathing noted in the rats who received aspartic acid and anesthetic was due to both a decrease of inspiratory and expiratory times. There was only a small increase of tidal volume in the group of rats that received aspartic acid. Interestingly, one rat "awoke briefly" after he got 250 mg/kg aspartic acid. Also rats that were given aspartic acid were under anesthesia for about one-half the time than rats who only received sodium pentobarbital. The results of this experiment differ from those in which unanesthetized male rats received aspartic acid. In those studies, rats who got 100mg/kg showed a stimulation of ventilation and metabolism, but those who got 580mg/kg had both depressed ventilation and metabolism lasting for over one hour. Thus, the present study suggests that there is a competitive interaction of aspartic acid and sodium pentobarbital on both ventilation and metabolism. Whether the increase of metabolism drives the increase of ventilation remains to be seen.

24.8

ACTIVITY OF AIRWAY SLOWLY ADAPTING RECEPTORS (SAR) FOLLOWING TOPICAL APPLICATION OF CAPSAICIN ON THE VAGUS NERVE. John T. Hatridge, F.B. Sant'Ambrogio and G. Sant'Ambrogio. Depts. of Physiology & Biophysics and Internal Medicine. The Univ. of Texas Medical Branch, Galveston, TX 77550.

We studied the effect of capsaicin applied on the vagus nerve on the activity of SARs. We performed experiments in 7 anesthetized, paralyzed, vagotomized, open-chested cats artificially ventilated with a constant volume respirator. We recorded from the peripheral cut end of the vagus nerve the unit activity of 14 SARs together with transpulmonary pressure. End-expiratory pressure was kept constant throughout the experiment. The average number of action potentials per breath was determined before and after 1% capsaicin (in Tween 80 and mineral oil) was applied on the vagus nerve caudad to the recording electrode. No significant changes in the number of action potentials in inspiration (T_I), expiration (T_E) and peak transpulmonary pressure (P_{TP}) were observed after 15 (T_I: 98.3 ± 3.5, T_E: 98.3 ± 8.5, P_{TP}: 101.1 ± 3.3; values are in percent of control ± SD, n=11) and 30 min (T_I: 95.6 ± 5.0, T_E: 97.4 ± 9.0, P_{TP}: 101.3 ± 3.9, n=10). For 2 SARs records were obtained also after 45 min; at this time the measured values were: T_I 97.2 ± 1.9%, T_E 102.6 ± 31.4% and P_{TP} 110.0 ± 1.0% of control. We conclude that topical capsaicin has no significant effects on transmission of nerve impulses in the myelinated fibers of SARs in the cat. (NIH Grant HL-20122)

24.9

CHARACTERISTICS OF WATER-RESPONSIVE LARYNGEAL RECEPTORS. J.W. Anderson*, F.B. Sant'Ambrogio, O.P. Mathew and G. Sant'Ambrogio. Departments of Physiology and Biophysics and Pediatrics, University of Texas Medical Branch, Galveston, Texas 77550.

Water-responsive laryngeal receptors (with fibers in the superior laryngeal nerve) were studied to characterize the specific physicochemical properties of water responsible for their stimulation. Receptor responses to water instilled into the isolated in situ larynx were studied in 8 anesthetized dogs breathing through a tracheostomy. Fifty-three receptors stimulated by water were also challenged with isoosmotic solutions of dextrose and sodium gluconate at 37°C. Receptors which only responded to water (n=31) with a long delay, long duration discharge were generally respiratory modulated. On the other hand, laryngeal receptors which responded to all test solutions (n=22) with a short delay, short duration discharge were generally non-respiratory modulated. We conclude that the former type of receptor responded to lowered osmolality, whereas the latter responded to the lack of chloride ion in the test solutions. These two types of receptors may be responsible for the cough and bronchoconstriction induced by inhaled aerosols of different ionic compositions (Am. Rev. Resp. Dis. 129:211, 1984).
Supported by NIH Grants HL-20122 and HL-32921; J.W.A. is a fellow of the Canadian Lung Association.

24.10

EFFECT OF L-MENTHOL ON LARYNGEAL COLD RECEPTORS. F.B. Sant'Ambrogio, J.W Anderson*, G. Sant'Ambrogio. Dept. of Physiology and Biophysics. The University of Texas Medical Branch, Galveston, Texas 77550.

We have studied the effect of L-menthol on laryngeal receptors. Experiments have been conducted in 4 anesthetized dogs breathing through a tracheostomy. We have recorded from 8 laryngeal cold receptors and 23 mechanoreceptors. Constant flows of air, between 17 ml/s and 200 ml/s, passing through the isolated upper airway in an expiratory direction, lowered laryngeal temperature (-1.84°C) and induced a rapidly adapting discharge of cold receptors that promptly ceased upon withdrawl of the airflow. Addition of L-menthol to the airflow evoked, for a similar decrease in temperature (-1.89°C), a greater activation of the cold receptors (36.1 ± 13.9 SD imp/s above control vs. 28.3 ± 17.6, $P < 0.01$). This activity still adapted rapidly in presence of airflow, but outlasted its cessation by at least 30 s. With menthol, 5 s after airflow withdrawal, the activity was 13.9 ± 9.4 imp/s above control *vs.* -1.2 ± 5.3 imp/s, at similar temperatures ($P < 0.01$). None of the 23 mechanoreceptors tested were affected by L-menthol. L-menthol constitutes a specific stimulant of laryngeal cold receptors and could provide an useful tool for studying their reflex effects.
Supported by NIH Grant HL-20122; J.W.A. is a Fellow of the Canadian Lung Association.

24.11

RESPONSES OF SLOWLY ADAPTING RECEPTORS (SAR) AND RAPIDLY ADAPTING RECEPTORS (RAR) TO PULMONARY VENOUS CONGESTION (PVC) BEFORE AND AFTER PLASMAPHERESIS (PP) IN RABBITS. M. Hargreaves*, K. Ravi* & C.T. Kappagoda, Dept. Med., Univ. Alberta, Edmonton, Canada.

The effect of PP on the responses of SAR and RAR to PVC was examined in anesthetized, artificially ventilated and open-chested rabbits. Two cannulae were inserted into the left atrium. One cannula was used for measuring left atrial pressure (LAP). The other, equipped with a balloon, was used to produce PVC. SAR (n=5) and RAR (n=5) activity was recorded from the right cervical vagus. After a 5 min control period, the LAP was increased by 5 and 10 mmHg, each for a period of 5 min. Then LAP was decreased to the control value for a final period of 5 min. PP was performed by withdrawing 10% of the blood volume. The stimulus-response relationship between increments in LAP and receptor activity was repeated.

Receptor Activity (impulses/min; mean ± S.E.M.)

LAP (mmHg)	Control	+5	+10	Control
SAR Pre.PP	2720±951	2821±957	3022±1074	2897±956
Post.PP	2786±815	2814±834	2854±822	2815±871
RAR Pre.PP	220±34	278±26	313±22	233±38
Post.PP	339±25	438±45	579±62	335±36

After PP, there was a significant elevation of the slope relating LAP and RAR activity ($p<0.01$). No significant change was noted in SAR activity. Thus, the RAR exhibit an enhanced sensitivity to PVC after PP.

24.12

RESPONSES OF SLOWLY ADAPTING RECEPTORS (SAR) AND RAPIDLY ADAPTING RECEPTORS (RAR) TO PULMONARY VENOUS CONGESTION (PVC) IN RABBITS. C.T. Kappagoda, M. Hargreaves* & K. Ravi*, Dept. Med, Univ. Alberta, Edmonton, Canada.

The responses of SAR and RAR to PVC in anesthetized, artificially ventilated and open-chested rabbits were examined. Two cannulae were inserted into the left atrium. One cannula was used for measuring left atrial pressure (LAP). The other, which was equipped with a balloon, was used to produce PVC by partial obstruction of the mitral valve. Afferent activity was recorded from the right cervical vagus. After a 5 min control period, the LAP was increased by 5 and 10 mmHg, each for a period of 5 min. Then, LAP was decreased to control and the neural activity recorded for a final control period of 5 min. The findings are summarised:

Receptor Activity (impulses/min; mean ± S.E.M.)

LAP (mmHg)	Control	+5	+10	Control
SAR (n=7)	1123±314	1190±331	1274±311	1100±299
RAR (n=12)	146±30	215±42*	296±548*	169±36

*$p<0.05$, compared to the other values, ANOVA.

Both SAR and RAR were located in the proximal airways. The results show that 1) PVC stimulates RAR, 2) a stimulus-response relationship exists between increments in LAP and RAR activity and 3) the SAR do not respond to PVC. It is suggested that the RAR are stimulated by fluid fluxes in the extravascular space of the proximal airways.

24.13

BEHAVIOUR OF RAPIDLY ADAPTING RECEPTORS (RAR) DURING PULMONARY EDEMA (PE) OF CARDIAC ORIGIN. K. Ravi* & C.T. Kappagoda, Dept. Med., Univ. Alberta, Edmonton, Canada.

The present study was designed to examine whether there is a sustained stimulation of RAR during PE produced by partial obstruction of the mitral valve (MVO). Experiments were performed on anesthetized, artificially ventilated and open-chested dogs. Two cannulae were inserted into the left atrium. One cannula was used for measuring left atrial pressure (LAP). The other, equipped with a balloon, was inflated with saline to produce MVO and raise mean LAP by 25 mmHg. RAR activity was recorded from the right cervical vagus. After a 5 min control period, LAP was raised by 25 mmHg above the control for a period of 45 min. RAR activity was recorded continuously. Extravascular lung water (ELW) was determined at the end of 45 min. The responses of RAR (impulses/min; n=8) are summarised:

	LAP (+25 mmHg)		
Control	First 15 min	Second 15 min	Third 15 min
75±20	348±53*	265±39**	223±30**

(*$p<0.05$, compared to the rest; **$p<0.05$, compared to the control and first 15 min values, ANOVA).

In 5 other RAR examined under control conditions, there was no significant change in activity over a period of 45 min. The ELW increased from 57±4% to 72±2% (n=5, $p<0.05$) during PE. The results show that during PE, there is a sustained stimulation of RAR with slow adaptation.

24.14

EXPIRATORY NEURON DISCHARGE RARELY MEDIATES SYMPATHETIC NERVE RESPONSE TO HYPERCAPNIA IN THE CAT. **W-X. Huang,* S. Lahiri, C. Di Giulio,* A. Mokashi,* A. K. Sherpa,* and Q. He.* Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6085.**

To test the hypothesis that sympathetic nerve response to hypercapnia during expiration depends on expiratory nerve activity, we studied responses of cervical preganglionic sympathetic nerve (PSN) activity, in relation to phrenic (PN) and internal intercostal expiratory (IICEN) nerve discharges in the anesthetized, paralyzed and artificially ventilated cats in which vagi and aortic nerves were cut bilaterally. PSN fibers with respiration-related activity were selected and their responses to hypercapnia during hyperoxia were studied. We found that, out of 21 IICEN fibers, 16 were stimulated and 6 were inhibited during hypercapnia (also inhibited during hypoxia) whereas all PN fibers were stimulated. The PSN fiber activity was stimulated during inspiration but only marginally during expiration. After carotid sinus nerve transection, IICEN fiber discharge decreased more than those of PN and PSN. Hypercapnia restored the IICEN discharge but PSN activity did not increase significantly during expiration. Thus, while the IICEN activity was dependent on intact carotid sinus nerves, the effects of central chemoreceptors on PSN activity during expiration were not mediated by the expiratory neurons in the cat. (Supported in part by grants NS-21068 and HL-19737)

24.15

SYMPATHETIC CHEMOREFLEX AND RECURRENT LARYNGEAL NERVE ACTIVITY IN RELATION TO RESPIRATORY DISCHARGE. **S. Lahiri, W. Huang*, A. Mokashi*, C. Di-Giulio* and Q. He*. Dept. of Physiol., Univ. of Penna. Sch. of Med., Philadelphia, PA. 19104-6085**

To test the possibility that sympathetic and laryngeal chemoreflexes are generated by the same respiratory drive we simultaneously studied chemoreflex responses of cervical preganglionic sympathetic nerve (PSN), phrenic nerve (PN), recurrent laryngeal nerve (RLN) and internal intercostal expiratory nerve (IICEN) activities in anesthetized, paralyzed and artificially ventilated cats. (1) 4/16 RLN single fibers discharged only during inspiration, 4/16 only during expiration, 7/16 showed peak activity during inspiration, diminishing in expiration, 1/16 peaked during expiration with weak activity during inspiration. (2) Like PN, the inspiratory RLN (I-RLN) fibers were always stimulated by hypoxia and hypercapnia and following cyanide and nicotine injections. (3) Hypocapnia abolished I-RLN activity as PN activity disappeared. (4) Two expiratory RLN (E-RLN) fibers were stimulated and another 2 inhibited during hypoxia. But all 4 were inhibited during hypercapnia. (5) E-RLN started firing and peaked at the beginning of postinspiration and fired in a decrementing pattern while most PSN fibers peaked during inspiration and fired in an augmenting pattern. (6) During hypocapnia, E-RLN activity increased whereas PSN activity diminished. Also, hypoxia which elicited PSN and PN responses inhibited E-RLN activity. Thus sympathetic and recurrent laryngeal chemoreflexes are not always mediated by the same respiratory drive. (Supported in part by grants NS-21068 and HL-19737)

24.16

MORPHINE INDUCED HYPERCAPNIA IN ANESTHETIZED SWINE, MONKEYS AND DOGS. E.P. Steffey, K.A. Jarvis, A.R. Elliott*, N. Willits* and M.J. Wolinet* School of Vet. Med. & Statistics Laboratory, Univ. of Calif., Davis, CA 95616

The increase in $PaCO_2$ caused by morphine (MOR) was evaluated in six adult mini-swine (S), rhesus monkeys (M), and dogs (D) anesthetized only with isoflurane (Iso) or halothane (Halo) in O_2. After determination of the minimum alveolar concentration of inhaled anesthetic preventing purposeful response to a tail clamp (MAC) MOR was injected IV (1 or 2 mg/kg). Anesthetic level was maintained relatively constant at MAC before and after MOR by adjusting alveolar anesthetic concentration in response to noxious stimulus. We found MOR increased $PaCO_2$ out of proportion to the level of anesthesia (Table 1). At the end of some studies naloxone was given and $PaCO_2$ returned to pre-MOR levels. We conclude: 1) MOR enhances respiratory depression during inhalation anesthesia, 2) the magnitude of this effect is similar in ISO anesthetized S, M and D, and 3) is similar with both Iso and Halo in D. (Support - NIH 2S07RR05457 & RR00169)

Table 1

		morphine (mg/kg)	$PaCO_2$ ($\bar{X}$ ± SE) Anesthetic	Anesthetic + morphine Overall[a]	Anesthetic + morphine Pre-Naloxone
Iso -	Swine	2	45.2 ± 2.2[c]	56.6 ± 2.1[a]	59.3 ± 1.9[a]
	Monkey	2	38.2 ± 2.3[c]	50.0 ± 3.4[a]	55.4 ± 6.4[a]
	Dog	2	46.3 ± 2.9[c]	55.8 ± 1.5[a]	57.4 ± 2.0[a]
	Dog	1	46.2 ± 2.4[c]	55.3 ± 2.1[a]	54.0 ± 2.4[a]
Halo -	Dog	1	42.2 ± 2.1[c]	55.6 ± 2.3[a]	55.1 ± 3.1[a]

[a]Average over 2 hrs for S & 4 hrs for others. [c,a]Values with superscript in common are not significantly different from each other with a level of significance of 0.05.

24.17

HYPERCARBIA ENHANCES CRICOTHYROID MUSCLE RESPONSE TO AIRWAY OBSTRUCTION. Gayle E. Woodson and Frank L. Powell. UCSD and VA Medical Center, San Diego, CA. 92161

Cricothyroid muscle (CT) contraction in inspiration is strongly recruited by negative upper airway pressure. Breathing air containing carbon dioxide also stimulates respiratory CT activity. To determine whether these effects are synergistic, integrated CT EMG activity was measured during unobstructed breathing and brief tracheal and upper airway occlusions (TO and UAO) in anesthetized dogs breathing room air, CO2 in air, and hypoxic air. For each dog, CT EMG was expressed as a percentage of the maximal observed activity. In all dogs, inspiratory CT EMG was highest during (UAO) with elevated blood levels of CO2. The average CT response to hypercarbic TO was 42.15%. Mean CT EMG values during room air UAO and TO were lower (52.3% and 21.5%). During hypoxia, CT responses to UAO and TO (42% and 20.1%) were not significantly different from those observed during room air breathing. The data suggest that hypercarbia, but not hypoxia, enhances CT response to airway obstruction.

24.18

BRAIN TISSUE ACIDOSIS AND VENTILATORY ACCLIMATIZATION TO HIGH ALTITUDE. S.Goldberg*, R.B.Schoene, D.Haynor*, B.Trimble*, E.Swenson, J.B.Morrison*, E.J.Banister*. Univ. of WA, Seattle, WA 98195 and Simon Fraser Univ., Burnaby, British Columbia, Canada V5A 1S6

In spite of a respiratory alkalosis, ventilation continues to increase upon ascent to high altitude for 7-10 days. The hypoxia-sensitive carotid body is partly responsible, but hyperventilation persists after removal of hypoxia. We hypothesized that a relative brain tissue acidosis accounted for part of the ventilatory adaptation. To evaluate this possible association, we performed ^{31}P magnetic resonance spectroscopy on the brains of four human subjects before and after 7 days at 14,000 feet (barometric pressure = 447 torr) in a hypobaric chamber. The results, in the table, suggest that the development of a brain intracellular acidosis may account in part for changes in ventilation at high altitude beyond those attributable to the carotid body.

Sea level	Pre ascent	Post descent
brain pH	7.01±0.032	6.98±0.036
blood pH	7.37±0.0245	7.435±0.037
blood pCO_2 (torr)	41.8±5.3	31.0±3.4

Supported in part by the American Heart Association and the Natural Sciences and Engineering Research Council of Canada.

24.19

GABA A RECEPTOR BLOCKADE AT THE INTERMEDIATE AREA (IA) OF THE VENTRAL MEDULLARY SURFACE (VMS) REVERSES CARDIORESPIRATORY DEPRESSION PRODUCED BY I.V. MIDAZOLAM. R.A. Gillis*, T.P. Abrahams,* S. Pineo,* P. Hamosh and A.M. Taveira da Silva. Georgetown University Sch. Med. Washington, D.C. 20007.

Drugs interacting with γ- aminobutyric acid (GABA)/ benzodiazepine receptors at the IA of the VMS cause cardiorespiratory depression. To determine whether application of the GABA A receptor antagonist bicuculline (B) to the IA of VMS reversed the cardiorespiratory depressant effects produced by intravenous (I.V.) midazolam (M) we administered M (2mg/Kg) to 8 pentobarbital (35mg/Kg i.p.) anesthetized cats while monitoring ventilation (VE), tidal volume (VT) respiratory rate (f) and blood pressure (BP). M decreased VE (-222±19 ml/m, $p<0.05$), VT (-9±2 ml, $p<0.05$) and BP (-36±13 mmHg, $p<0.05$). Application of B (10 ug/side) to the IA of the VMS caused an increase in VE (+153±17 ml/m, $p<0.05$), VT (+9±2 ml, $p<0.05$) and BP (+20±4 mmHg, $p<0.05$). In contrast, B failed to reverse the decrease in VE (-294±64 ml/m, $p<0.05$) produced by I.V. morphine (1mg/Kg, N=3), while application of Naloxone (15ug/side) to the IA of the VMS returned VE (+258±38 ml/m, $p<0.05$) to control values. We conclude that I.V. M depresses cardiorespiratory activity through a GABAergic mechanism at the IA of VMS.

Supported by MH 42322.

24.20

WITHDRAWN

24.21

MECHANISMS OF CIGARETTE SMOKE-INDUCED STIMULATION OF RAPIDLY ADAPTING RECEPTORS IN THE CANINE LUNGS. Y. R. Kou and L.-Y. Lee. Univ. of Kentucky, Lexington, KY 40536.

Stimulation of rapidly adapting receptors (RARs) evoked by cigarette smoke (CS) consists of an immediate and a delayed response (Physiologist 31: A171). To investigate the mechanisms of the stimulation, we recorded the afferent activity of RARs from vagal filaments and delivered a single breath (b) (120 ml) of CS in anesthetized, open-chest and artificially ventilated dogs. Studies were repeated after a pretreatment with either aerosolized hexamethonium (HEX) (3-8 b, 10%) or isoproterenol (ISO) (12-15 b, 2%). The immediate response to CS (17.7 ± 3.4 imp/b; mean ± SE; n = 9) was completely abolished by HEX (0.6 ± 0.2 imp/b), but the delayed response was not affected in the 11 RARs studied in 9 dogs. In contrast, the immediate response (7.3 ± 1.8 imp/b; n = 10) was not affected by ISO (6.3 ± 1.8 imp/b), but the delayed response (6.0 ± 0.6 imp/b) was significantly attenuated (3.4 ± 0.9 imp/b) in the other 15 RARs studied in 10 dogs. The elevation of pulmonary resistance induced by CS, coinciding with the delayed stimulation of RARs, was reduced to 41.9% by HEX, but was abolished by ISO (6.7%). These results suggest that nicotine is responsible for eliciting the immediate stimulation while the bronchoconstriction may play a part in evoking the delayed effect of CS on RARs.

(Supported by KTRB grant 41066 and NIH PPG grant 40369).

25.1

NONINTERACTION OF BARORECEPTORS AND CHEMORECEPTORS IN THE CONTROL OF PLASMA RENIN ACTIVITY RESPONSES TO FETAL HYPOXIA. Charles E. Wood and Hershel Raff. Department of Physiology, Univ. Florida Coll. Med., Gainesville, FL 32610.

Fetal hypoxia stimulates reflex increases in mean arterial blood pressure and decreases in fetal heart rate, but very small increases in plasma renin activity (PRA). This study was designed to test the hypothesis that the increase in mean arterial blood pressure secondarily inhibits the PRA response to hypoxia. Seven fetal sheep (115-127 days' gestation) and their mothers were chronically prepared with amniotic fluid catheters and fetal and maternal arterial and venous catheters. Each fetus was studied twice: once subjected to hypoxia with control and once without control of mean arterial pressure (intravenous infusion of sodium nitroprusside). Maternal ventilatory hypoxia decreased fetal P_aO_2 from 24.8±1.2 and 24.3±0.8 mm Hg to 13.9±0.8 and 15.6±1.2 mm Hg ($p<0.05$) in the uncontrolled and controlled groups, respectively. Fetal P_aCO_2 decreased from 42.3±0.9 and 42.0±1.0 to 39.9±0.8 and 40.3±0.6 mm Hg in the two groups ($p<0.05$). Mean arterial blood pressure increased from 45.6±2.3 to 50.1± 3.0 in the uncontrolled group and remained constant (43.1±2.1 to 42.5± 2.7 mm Hg) in the controlled group. PRA increased from 3.32±0.76 and 3.30±0.85 to 3.98±0.71 and 4.62±0.89 ng Ang I/ml·hr ($p<0.05$) in the uncontrolled and controlled group, respectively. These responses were not different from each other (p=NS). We conclude that there is no interaction between chemoreceptors and arterial baroreceptors in the control of the PRA response to hypoxia in fetal sheep. (Supported by HL36289. CEW is an Established Investigator of the American Heart Association.)

25.2

DEVELOPMENTAL PATTERNS OF RAT BRAIN ANTIOXIDANT ENZYME ACTIVITY: RESPONSE TO NORMOBARIC HYPEROXIA. W.H. Drummond, L. Frank and D.J. Massaro. U. of Florida and U. of Miami, Coll. Med., Pulmonary Research Lab, VAMC, Miami, FL.

Mammalian tissues are protected from toxic effects of oxygen free radicals by inducible antioxidant enzymes (AOE): superoxide dismutase (SOD), catalase (Cat) and glutathione peroxidase (GP). Lung antioxidant enzyme activity rises before birth, protecting newborns from hyperoxia after birth. Hyperbaric hyperoxia is toxic to adult lungs and brains. We hypothesized that infant brains, like infant lungs, might have altered sensitivity to oxygen damage. Rat pups age 2 to 14 days, adults and controls were exposed to FiO_2 = .97 or air for 72 hours, then the brains weighed, homogenized, and assayed for AOE activity, protein and DNA. Hyperoxic exposure in pups slowed brain and body growth ($p<.05$, ANOVA). Brain DNA content rose immediately after hyperoxia in adults and pups, but fell in adult hyperoxia survivors sacrificed after 10 days. Basal brain catalase activity was 2-fold higher in pups and increased after oxygen ($p<.001$), unlike adults. Pup brain SOD activity was half adult levels ($p<.001$); pup brain GP was about 70% of adult. Neither enzyme changed after oxygen exposure. We found developmental differences in basal brain antioxidant enzyme activity in rats. Brain catalase activity is increased in rat pups after normobaric hyperoxia. Adult brains show less inducibility of antioxidant enzyme activity.

25.3

DIRECT FETAL UPTAKE OF ^{22}Na AND DIGOXIN FROM AMNIOTIC FLUID (AF). Harriet S. Iwamoto, Kuni Hamamoto,* and Abraham M. Rudolph. UCSF, San Francisco, CA 94143

The composition and volume of AF is commonly perceived to reflect a balance of fetal urine and lung fluid production and fetal swallowing. However, changes in ingestion do not alter urine or lung fluid production. To investigate whether an alternate route exists for AF movement, we measured uptake of $^{22}NaCl$ injected intra-amniotically in 4 esophageal-ligated fetal sheep at 129-130 d gestation, 8-10 d after surgery. Samples were obtained from AF (2-3 sites) and fetal (F) and maternal (M) arterial blood for 6 h. pH, PO_2 and PCO_2 in F were initially 7.38 ± 0.03 (mean ± SD) and 23 ± 6 and 51 ± 4 torr and did not change. ^{22}Na uptake into F, evident by 10 min after injection, was a linear function of time (slope = 2.0 ± 1.3, $p < 0.0001$) whereas uptake into M was minimal (slope = 0.08 ± 0.13). To determine whether Na^+K^+-ATPase was involved, we administered digoxin (0.12 mg/kg injection; 8 mg/h infusion) intra-amniotically beginning 1 h before ^{22}Na administration. Digoxin immunoreactivity in F rapidly increased from undetectable levels and plateaued at 2.2 ± 1.2 ng/ml but remained undetectable (< 0.18 ng/ml) in M. Digoxin increased the volume of distribution for Na within the maternal-fetal unit but did not alter fetal Na uptake. These data suggest that Na is taken up into F directly from AF by a passive mechanism via a pathway other than fetal swallowing or M-F placental transfer. Possible pathways include uptake into small fetal vessels that perfuse the fetal membranes or placental surface. These data also demonstrate that intra-amniotic administration of digoxin increases concentrations in F to values within the therapeutic range without increasing concentrations in M. Supported in part by NIH grant GM26691.

LIPID, CARBOHYDRATE, AND CALCIUM METABOLISM

26.1

THE VASCULAR EFFECTS OF OMEGA-3 POLYUNSATURATED FATTY ACIDS. Mary B. Engler. UCSF, San Francisco, CA 94143-0610

Recent human and animal studies have indicated dietary supplementation of omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may be preventive and/or protective against cardiovascular disease. The direct vascular effects of DHA and EPA on smooth muscle tone were evaluated using rat aortic rings. Aortic rings were isolated and fixed in a smooth muscle bath to an isometric force-displacement transducer. The rings were equilibrated for 60-90 minutes in Krebs-Ringer bicarbonate buffer (pH 7.4) and gassed continuously with 95% O_2, 5% CO_2 at 37±0.5°C. A time-and concentration-dependent relaxation was observed for DHA and EPA in phenylephrine precontracted vessels. The relaxation induced by DHA and EPA (1-255uM) developed slowly reaching maximum within 25 minutes. Significant DHA relaxation was noted at concentrations from 1uM (7±2%) to 255uM (61±4%). The relaxation induced by EPA was significant starting at 31uM (18±1%) up to 255uM (63±4%). The maximum relaxation response to EPA was 129±17% at 1550uM and 122±10% at 755uM for DHA. Removal of the endothelium, or the use of cyclooxygenase and lipoxygenase inhibitors did not significantly alter the DHA- or EPA- induced responses. The beneficial cardiovascular effects attributed to the omega-3 fatty acids may, in part, be due to the direct actions of DHA and EPA on the vessel wall.

26.2

DIETARY GAMMA-LINOLENIC AND ALPHA-LINOLENIC ACID-INDUCED FATTY ACID CHANGES IN PLATELETS AND AORTA OF THE RAT: EFFECT OF ETHANOL. Marguerite M. Engler. Univ. of California, San Francisco, CA 94143-0610.

Effects of dietary gamma-linolenic (18:3n-6) and alpha-linolenic acids (18:3n-3) and ethanol exposure on aortic and platelet fatty acid levels were studied in male Sprague-Dawley rats. Animals were fed a fat-free diet supplemented with 11% (wt/wt) of either sesame oil (SES, 18:1n-9), borage oil (BOR, 18:3n-6), or linseed/safflower oil (LO/SO, 18:3n-3) for 7 wks. Animals were subsequently exposed to ethanol vapors by inhalation the last 6 days of the dietary treatments. Moderate blood ethanol levels (118±6.6 mg/dl) were obtained. As a result of BOR feeding, proportions of n-6 fatty acids (18:3n-6, 20:3n-6, 20:4n-6) increased in the platelets and aorta. Animals on the LO/SO diet had increased levels of n-3 fatty acids (18:3n-3, 20:5n-3, 22:6n-3). Following ethanol exposure, 20:3n-6 content increased in the BOR-fed rats and remained unchanged by feeding the SES or LO/SO diets. The 20:4n-6 content in the platelets decreased in the animals fed the SES or LO/SO diets and was unchanged in the BOR-fed group. These results suggest that dietary n-6 and n-3 fatty acids influence fatty acid composition in vascular tissue and platelets. In addition, BOR feeding inhibits ethanol-induced depletion of 20:4n-6 in platelets. BOR may be an effective nutritional approach for treatment of disorders in fatty acid metabolism associated with alcoholism.

26.3

EFFECT OF PROSTAGLANDIN E1 (PGE1) ON 123I-LOW DENSITY LIPOPROTEIN (LDL) APO-B,E-RECEPTOR BINDING. Helmut Sinzinger, Irene Virgolini, Shuren Li, Graziana Lupattelli, Waltraud Rogatti. Atherosclerosis Research Group Vienna and Department of Nuclear Med. University of Vienna, Vienna, Austria.

Although a beneficial effect of PGE1 on vascular smooth muscle cell lipid metabolism has been reported, investigations examining the influence of PGE1 on liver-LDL-receptors are lacking sofar. This study investigated the effect of PGE1 on LDL apo-B, E-receptors in human, rat and swine liver. PGE1 significantly decreased the amount of unlabelled LDL necessary to inhibit 123I-LDL-binding in all liver preparations of the three species in a dose-dependent manner ($p<0.01$-0.001) with an ED-50 value of approximately 50 µmol/l. In absence of PGE1 the number of LDL-receptors calculated for human, rat and swine liver amounted to 138±15, 136±11 and 35±6 µg protein/mg liver protein, respectively. In presence of 50 µmol/l PGE1 the number of LDL-receptors was significantly ($p<0.001$) increased and amounted to 309±29, 321±31 and 78±12 µg protein/mg liver protein, respectively.

It is concluded that PGE1, beside its clinical benefit in the treatment of peripheral vascular disease, may have a regulatory (?) role in lipid metabolism.

26.4

123I-LOW-DENSITY LIPOPROTEIN (LDL) APO-B,E-LIVER RECEPTOR IMAGING IN HUMAN. Graziana Lupattelli, Irene Virgolini Johann Pidlich, Peter Angelberger and Helmut Sinzinger. Dept. of Nuclear Medicine, University of Vienna and 2nd Dept. of Internal Medicine, University of Perugia, Italy.

LDL were isolated by ultracentrifugation or immunoaffinity chromatography from normolipemic patients (n=10), from patients affected by familial hypercholesterolemia (n=6) and from patients affected by other kinds of hyperlipoproteinemia (n=12, HLP) and labelled with 3 mCi 123I using iodogen or iodine monochloride. After reinjection of autologous 123I-LDL dynamic imaging was performed over the liver, precordium and lungs for 30 minutes using 1 frame/30 seconds. The liver volume and the total tracer uptake over the liver was determined by a specific computer program using various views from S.P.E.C.T-scintigraphy (30 seconds/angle) and a whole body image. Liver/lung and liver/heart ratios were decreasing during the first 30 minutes only in patients with familial hypercholesterolemia whereas they increased in normolipemics and in patients affected by others kinds of HLP.

This method may be a new approach for studying the liver LDL-receptor in vivo and thus for evaluation of diet or drug therapy in patients with familial hypercholesterolemia.

26.5

BREATH ETHANE PRODUCTION IN COPPER-DEFICIENT RATS. J.T. Saari and M.P. Habib. USDA, ARS, Grand Forks Human Nutrition Research Center, Grand Forks, ND 58202, and Department of Internal Medicine, Tucson Veterans Administration Medical Center, Tucson, AZ 85723.

Evidence is accumulating which indicates that Cu-deficient animals are prone to oxidative damage. To further investigate this possibility we measured the production of breath ethane, a hydrocarbon by-product of lipid peroxidation, in Cu-deficient rats. Male, weanling, Sprague-Dawley rats were fed either a purified diet which was deficient in Cu (CuD) or the same diet supplemented with 5 ppm Cu (CuS). After 33-34 days the rats were individually placed in gas-tight metabolic cages through which ethane-free air or 100% O_2 was passed. Expired ethane was adsorbed onto cold activated charcoal, liberated by heating and measured by gas chromatography. Cu deficiency was verified by lung and liver Cu content and by serum ceruloplasmin concentration. Ethane production rates (pmoles/min/100 g ± SE) were 3.3 ± 0.3 (CuS-air), 4.3 ± 0.5 (CuD-air), 8.3 ± 0.8 (CuS-O_2) and 12.2 ± 1.4 (CuD-O_2). Analysis of variance indicated that both Cu-deficiency ($p<0.01$) and breathing 100% O_2 ($p<0.0001$) enhanced ethane production, with no interaction between treatments. This finding complements prior evidence that increased lipid peroxidation occurs in Cu-deficient rats.

26.6

EFFECT OF COLD EXPOSURE ON THE KINETICS OF TISSUE VITAMIN E UPTAKE AND DEPLETION IN THE RAT. Willy A. Behrens* and Rene Madère* (SPON: D.O. Foster) Food Directorate. Health Protection Branch. Tunney's Pasture. Ottawa, Ontario. Canada. K1A OL2.

Vitamin E was estimated in plasma and tissues of rats kept for 3 months on 1)low vitamin E diet and 2)high vitamin E diet. Some of the animals from each group were switched to the opposite diet and the kinetics of uptake and depletion of vitamin E were followed 3, 8 and 15 days after diet change. Some rats were also submitted to cold exposure (6-8° C) for three days. Plasma, red blood cells, liver and spleen were the only tissues that responded rapidly to the diet change; after three days their vitamin E levels corresponded to those of the new diet. Heart, brain, lung and muscle were slow in reacting to diet change. Fifteen days after the change in diet, white adipose tissue did not respond. Cold exposure for three days did not produce any significant change in the vitamin E content of any tissue, indicating despite high oxygen consumption by the animal, vitamin E was not consumed or mobilized.

26.7

THE ROLE OF ACETYL-COA IN DETERMINING TCA CYCLE FLUX PATTERNS IN AS-30D HEPATOMA CELLS. Anne L. Holleran*, Gary Fiskum* and Joanne K. Kelleher. George Washington Univ. Med. Ctr., Washington, D.C. 20037

Unlike normal liver, hepatoma cells are known to utilize acetoacetate which may be a major source of acetyl-CoA. Experiments were conducted to examine what role is played by compounds which increase flux to acetyl-CoA. AS-30D cells were incubated with [6-^{14}C]glucose, 6mM glucose, 0.75mM glutamine and either 2mM dichloroacetate (DCA) or 2mM acetoacetate. Cells incubated with DCA, an activator of pyruvate dehydrogenase (PDH), incorporate 50% more ^{14}C into lipid than under control conditions but a 100% more ^{14}C into CO_2. Cells incubated with acetoacetate, an inhibitor of PDH flux, incorporate less ^{14}C into lipid than under control conditions but show a three fold increase in CO_2 production. The observed increase in $^{14}CO_2$ production could have one or more explanations. Oxidation of acetoacetate may stimulate the TCA cycle causing greater flux of acetyl-CoA to CO_2. Acetoacetate may change the degree to which four or five carbon units leave the TCA cycle. Evidence for these two explanations is that acetoacetate increases oxygen consumption and decreases the acetate $^{14}CO_2$ ratio. Other possible explanations include $^{14}CO_2$ production via pyruvate carboxylation pathways, the pentose phosphate pathway and cholesterol synthesis. These studies demonstrate the use of CO_2 ratios in evaluating flux into the TCA cycle. Supported by NIH grant GM33536.

26.8

HEXOKINASE DISTRIBUTION IS MODULATED IN CULTURED SMOOTH MUSCLE CELLS. R.M. LYNCH AND F.S. FAY, Dept. Physiology, Univ. Massachusetts Medical Center, Worcester, MA 01655.

Using immunocytochemical techniques, hexokinase (HK) is found to be associated with mitochondria in the A7R5 smooth muscle cell line. It is proposed that this specific localization is influenced by the metabolic state of the cell. To test this hypothesis, we have made a fluorophore labeled HK which maintains its native catalytic and binding activities Immediately following microinjection, the fluorescent HK is uniformly distributed throughout the cell, as observed by digital imaging microscopy. However within 10 minutes, the HK localized into punctate structures which were identified as mitochondria by colabeling with rhodamine 123. Incubation of HK with a monoclonal antibody to the domain responsible for binding to mitochondria blocks HK localization. Glucose catabolism was inhibited using 2-deoxyglucose (2DG), in an attempt to alter the localization of HK. Within 5 minutes of incubation with 2DG, a significant amount of HK moved off of mitochondria. Our findings demonstrate that HK is localized to mitochondria in living A7R5 cells, and altering metabolic rate effects this enzyme distribution. These observations support the hypothesis that specific glycolytic enzymes are non-uniformly distributed within the cytosol, and that their distribution is dynamically regulated. This work is funded by a Charles A. King Fellowship (RML), and NIDDK DK32520 to the Diabetes and Endocrinology Research Center, of U. Mass.

26.9

CALCIUM CHANNEL ANTAGONIST VERAPAMIL REDUCES BONE LOSS INDUCED BY LOW-CALCIUM DIET IN RATS.
Samarendra N. Baksi and Robert C. Speth*, Department of VCAPP, Washington State University, Pullman, WA 99164-6520

The calcium (Ca) ion is vital to bone formation and regulation of parathyroid hormone (PTH) secretion. Drugs which influence Ca channels also regulate PTH secretion, but their effect on bone mineralization is unknown. This study tested the hypothesis that chronic treatment with verapamil prevents or reduces bone loss induced by a low-Ca diet. Four-week-old male rats were divided into 6 groups (5 to 8 rats/group). Two groups received a diet containing either normal (1.4%), low (0.005%) or high (2.8%) Ca and 0.5% phosphorus (P). One of each diet group was injected subcutaneously with either verapamil (0.5 mg/kg) or vehicle daily. After 8 weeks the left femur and second lumbar vertebrae were processed for dry weight, density and ash determinations. Sera were analyzed for total and free Ca, inorganic P and PTH. The results indicate that verapamil treatment significantly increased dry weight (17%), density (12%) and ash content (43%) in the femur compared to respective vehicle-treated rats on low Ca. In vertebrae, a corresponding increase was found only in density (10%) and ash content (20%). This protective effect was not seen in normal or high Ca groups. Although serum Ca, P and PTH levels were affected by various diets, they were not significantly influenced by verapamil treatment. Data indicate that verapamil inhibited low Ca-induced bone resorption by an unknown mechanism (Supported by Farrell Fund and NIH NS 21305).

26.10

DEPOSITS OF CRYSTALLINE MATERIAL CONTAINING SILICON IN SURGICALLY EXCISED NATURAL AND BIOPROSTHETIC VALVES
Paul D. Stein, Chin-Hua Wang,* Jeanne M. Riddle,* Hani N. Sabbah, Douglas A. Stein,* Donald J. Magilligan, Jr. Henry Ford Heart and Vascular Institute, Detroit, MI. 48202

Ninety-seven surgically excised natural valves (33 mitral, 63 aortic, 1 tricuspid) and 35 degenerated porcine bioprosthetic valves (27 mitral, 8 aortic) were examined by scanning electron microscopy and x-ray energy spectroscopy to assess the occurrence of crystalline deposits containing silicon (Si). To reduce the possibility of surface contamination, the deep layers of some valves were examined after exposure by fracture of the leaflets. In both natural valves and porcine bioprosthetic valves, crystalline material containing Si was observed in the deep tissue entwined within subendothelial fibers. Among natural valves, Si was present in 34 of 97 (35%). Among the 34 natural valves that showed Si, 24 (71%) also showed microdeposits of calcific material. Among the degenerated porcine bioprosthetic valves, 4 of 35 (11%) showed Si. Silicon participates in the calcification of bone, and is found in the intima of the aorta and large arteries. These observations raise the possibility that Si may participate in the dystrophic calcification of natural valves and porcine bioprosthetic valves.

26.11

COCAINE, CATECHOLAMINES AND CALCIUM HOMEOSTASIS
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Selected calcium channel antagonists such as nitrendipine, diltiazem, flunarizine, will prevent cocaine induced cardiac lesions and lethality in the rat administered 60mg/kg intraperiteonally. This dose will produce in control animals behavioral and cardiovascular anomalies, convulsions and death in an average time of 10 min (LD_{100} 10_{min}) The selected antidotes are administered 5 min. after the lethal dose of cocaine. (FASEB J. 3:A1380,1988). In the present study 24 rats were fitted under anesthesia with catheters in the caudal and carotid arteries. 0.8 ml of blood was withdrawn from the carotid catheter, and this volume was immediately replaced by dextran. Samples were taken 5 min. before cocaine intoxication as well as 5 and 10 minutes after. Catechols were measured in plasma by the radioenzymatic method. Following cocaine intoxication significant increments in dopamine, norepinephrine and mostly epinephrine were observed in control animals. Five min. after onset of nitrendipine treatment, (7.2ug loading dose and 1.2ug/kg min) concentration of catecholamine were significantly lower from thoseof the untreated animals sampled at that time, and close to control. Cocaine releases significant amounts of catechols from the adrenals, which could account for the acute cardiac toxicity attributed to this drug. Selected calcium channel antagonists, by preventing this release, restore circulatory and hormonal homeostasis.

GASTROINTESTINAL EPITHELIUM

27.1

cAMP ANALOGUES IN RAT PANCREATIC ACINI AFFECT CHOLECYSTOCHININ (CCK-8) BUT NOT CARBAMYLCHOLINE (CCH) INDUCED INTRACELLULAR Ca++ TRANSIENTS.
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The effect of the cAMP analogues 8-(4-chlorophenylthio)adenosin 3':5'-cyclic monophosphate (cptcAMP) and of 8-bromoadenosin 3':5'-cyclic monophosphate (brcAMP) on CCK and CCH induced Ca++ transients has been evaluated on rat pancreatic acini, enzimatically and mechanically dissociated. For intracellular Ca++ measurements, isolated acini from one pancreas were loaded with the Ca++ sensitive dye fura-2 (1 um), for 30 min at 37C under continuous oxygenation. Fluorescence of fura-2 was measured (excitation and emission wavelenghts respectively 340 and 510 nm) at 37 C in 1.5 ml of stirred acini suspension in a Krebs-Henseleit modified medium containing 1.25 mM Ca++, using a custom-built fluorimeter. [Ca++]i was calculated according to Tsien et al. We found that: 1) both cptcAMP (25-100 um) and brcAMP (500-2,000 mM) do not cause by themselves any change of the basal [Ca++]i, nor modify the ionomycin (0.1-2um) induced Ca++ transient; 2) both cptcAMP (25-100um) and brcAMP (500-2,000 mM) administered 30-45 sec before CCK-8 (0.3-3 nm) enhance the response to a subsequent (30-60sec) dose of either CCK-8 or CCH (0.3-3 mM), the former being more effective than brcAMP; the effect shows a dose-response relationship; 3) both cptcAMP and brcAMP administered 30-60 sec after CCK-8 cause a transient (30-60 sec) decrease of the [Ca++]i and the administration of CCK or CCH during this phase evokes a Ca++ transient whose magnitude is higher than that measured at the same time intervals in absence of the cAMP analogues; 4) neither the first nor the second described effect of the cAMP analogues on CCK induced Ca++ transient were observed performing the experiments with CCH dose (0.3-3 mM) producing the same intracellular Ca++ peak evoked by 0.3-3 nm CCK-8. Therefore: 1) cAMP analogues seem to modulate intracellular Ca++ mobilization induced by CCK-8 at a step preceding the intracellular Ca++ stores depletion; 2) the lack of effect on equivalent doses of CCH suggests a partially different pathway of activation of phospholipase C following receptor activation.

27.2

SINGLE CHANNEL ANION CURRENTS ACROSS THE APICAL MEMBRANES OF RABBIT PARIETAL CELLS.
Richard L. Shoemaker, Christos G. Psarras* and Gaetano Saccomani*. Dept. of Physiology & Biophysics, Univ. of AL at Birmingham, Birmingham, AL 35294

Parietal cells were isolated from rabbit mucosa and purified by Nycodenz gradient. Cells were plated on Matrigel-coated cover slips and incubated in DME/F-12 medium at 37°C for 18 to 48 hours. Glass pipettes (#8161) were filled with (in mM): 150 NMDG Chloride, 2 $CaCl_2$; the bath contained 150 NaCl, 5 HEPES, 1 $MgCl_2$, 1 EGTA, 0.4 $CaCl_2$. Cells were patched on the apical surface under resting conditions (10^{-4}M cimetidine); in 11 out of 13 patches, no channels were observed either in cell attached (C/A) or inside out (I/O) mode. Cells stimulated by the combination of 10^{-4}M histamine, 10^{-3}M db-cAMP and 10^{-3}M IMX for 30 minutes at 37°C and then patched, channel activity was seen in 36 of 65 C/A patches and in 27 of 52 I/O patches. A flickering type channel, outwardly rectified with 55±5pS conductance was seen most often. This channel was permeable to other anions. The P_o and conductance was reduced by DCP. Other anion channels were seen also. NIH Support.

27.3

INTRAGASTRIC FOOD BUT NOT GASTRIC DISTENTION INDUCES JEJUNAL WATER SECRETION IN THE ANESTHETIZED FERRET. J. Auchampach and B. Greenwood. (SPON: G. M. Pieper) Dept. of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI 53226.

Previous studies in our laboratory demonstrated that feeding conscious ferrets induces an immediate increase in jejunal transmural potential difference (PD), an indicator of electrogenic ion transport. This epithelial response induced by feeding could be reproduced in the anesthetized ferret by intragastric food. The aims of the present study were to examine in the anesthetized ferret: 1) whether the food-induced rise in PD represents an increase in water secretion and 2) whether activation of gastric mechanoreceptors by gastric distention, in the absence of food, is the stimulus that alters jejunal epithelial activity. Anesthetized ferrets were given either intragastric food (4gm of ground Purina Cat Chow in 15ml of water) or gastric distentions with air while monitoring jejunal PD and water transport. Jejunal PD was measured by connecting two agar salt bridges via calomel half-cells to an electrometer. Changes in water transport across a 10cm segment of jejunum was measured using the non-absorbable marker perfusion technique. In three animals, intragastric food increased jejunal PD from -2.4 to -9.8mV and converted jejunal water transport from basal net absorption of 29±12µl/gm dry wt/min to a net water secretion of 86±31µl/gm dry wt/min. Step gastric distentions (50ml in 5 sec) and ramp distentions (10ml/min up to 50ml), a physiologic rate of inflation, induced no changes in electrogenic epithelial transport. Therefore, we conclude that intragastric food, but not activation of gastric mechanoreceptors by gastric distention, stimulates net jejunal water secretion in the anesthetized ferret.

27.4

THE EFFECT OF GASTRIC MUCOSAL BLOOD FLOW(GBF) ON GASTRIC POTENTIAL DIFFERENCE(GPD) L.E. Wittmers*,A. Alich*, L. Anderson*, and L.Semenchuk*, (SPON: G. Marchand) Department of Physiology University of Minnesota-Duluth School of Medicine and Department of Chemistry College of St. Scholastica Duluth MN 55812

A potential difference normally exists across the gastric mucosa. The magnitude of the GPD is thought to be a function of the mucosal barrier's integrity. Mechanisms governing changes in GPD are not well known. Recently we observed that decreases in GPD were associated with spontaneous decreases in systemic blood pressure. Therefore we have studied the relationship between GPD and GBF. Anesthetized Sprague-Dawley derived rats were instrumented with carotid artery and jugular venous catheters, electrodes in the spleen and stomach for measurement of GPD and a laser doppler probe attached to the sersoal surface of the gastric wall for measurement of GBF. Stepwise decreases in GBF were induced by iv injection of Epinephrine (2.5, 3.3, 5.0,8.0 and 25.0x10^{-3} mg/Kg). There was a progressive decrease in GPD and GBF with increasing doses of Epinephrine. The GPD paralleled GBF and recovered to control levels as the GBF recovered. In conclusion, changes in GPD may be induced by alterations in GBF without damage to mucosal barrier integrity. Supported in part by the Miller Dwan and the Duluth Clinic Foundations.

27.5

COMPARISON OF PORCINE PROXIMAL JEJUNAL MUCOSA (MUC) AND SMOOTH MUSCLE (SM) NEUROKININ (NK) RECEPTORS. A.M. Parsons*, J. Vogt* and D.R. Brown*. (SPON: S.M. O'Grady). Dept. of Vet. Bio., U of M, St. Paul, MN 55108

The undecapeptide substance P (SP) and the decapeptides NKA and NKB have been reported to reside in neurons intrinsic to the small intestine. In this study, we examined and compared NK receptors mediating MUC ion transport and SM contractility in the porcine proximal jejunum. MUC was separated from SM by blunt dissection and mounted in Ussing chambers. SM was cut into strips oriented longitudinally and suspended isometrically in organ baths. The relative order of peptide potency in elevating MUC short-circuit current (I_{sc}) and in increasing SM contractions were similar with SP > NKA >> NKB; NK ED_{50}'s for elevating I_{sc} were 17, 65 and 1500 nM and 13, 31 and 133 nM for increasing SM contractility, respectively. On the other hand, the order of efficacy was SP = NKA = NKB in MUC and NKA > SP = NKB in SM. In MUC, the neuronal conduction blocker tetrodotoxin (0.1uM) did not inhibit I_{sc} responses to SP indicating that SP acts directly on epithelial cells to produce its effects. SP exhibited autotachyphylaxis, but was not tachyphylactic to NKA. NKA actions, however, were inhibited after SP. No cross tachyphylaxis occurred between SP and NKB. We hypothesize that NK peptides interact with similar target cell receptors in both preparations.

27.6

ENDOGENOUS NEUROTRANSMITTERS ALTER ION TRANSPORT IN PORCINE DISTAL JEJUNUM(DJ). Keith R. Hildebrand* & David R. Brown. Dept Vet Biol, U of M, St Paul, MN 55108

Regulation of ion transport by enteric neurons in mammalian small intestine is not well understood. We examined the role of acetylcholine(ACh) and norepinephrine(NE) in ion transport induced by transmural electric field stimulation (EFS) in the porcine DJ in vitro. Muscle-stripped DJ mucosa was mounted in Ussing chambers and optically-isolated, rectangular-wave pulses(300) of 0.5msec duration were delivered to each tissue at 0.5 and 10 Hz. EFS evoked a rapid transient increase in Isc of 29.3±7.2 and 46.3±9.2 µA/cm^2 respectively above basal levels. EFS-evoked Isc increases (EEII) were inhibited by tetrodotoxin (0.1µM), a neuronal Na channel blocker. The muscarinic antagonist, atropine (1µM), decreased EEII by 45% at both frequencies. Control tissues stimulated simultaneously with atropine-treated tissues exhibited no significant diminution of EEII upon repeated stimulation at either frequency. NE produced a dose-dependent inhibition of EEII with an EC_{50} = 20nM and complete inhibition at 10µM. Phentolamine, a nonselective α-adrenergic antagonist, had no effect on EEII alone but at 1µM produced a 10-fold dextral shift in the NE dose-response curve. These results suggest that (i) neuronal ACh acting at muscarinic receptors mediates a portion of the EEII, and (ii) NE inhibits EEII via an α-adrenergic mechanism.

27.7

ACETYLCHOLINE (ACH) AND THE NEUROREGULATION OF ION TRANSPORT IN PORCINE PROXIMAL JEJUNUM (PJ). R. Chandan* and D.R. Brown. Department of Veterinary Biology, University of Minnesota, St. Paul, MN 55108.

Ion transport in the intestinal epithelium appears to be controlled by enteric neurons. Electrical field stimulation (EFS) of rodent gut mucosa has been found to produce elevations in short-circuit current (Isc) due in part to neural ACH release. In this study, we examined the role of ACH in the phasic neuronal control of ion transport in the porcine PJ.EFS(100 pulses at 10 Hz,0.5 msec. pulse width, 30 V/cm^2) was delivered to muscle-stripped sheets of PJ mucosa-submucosa mounted in Ussing chambers. EFS elevated Isc by 15 ± 3 µA/cm^2; this response did not decrease after multiple stimulations but was abolished by tetrodotoxin (TTX,0.1µM). EFS-induced Isc was decreased 43 and 68% by 10 µM hexamethonium (HEX) or 1 µM atropine (ATR), respectively (n=6 tissues each, p 0.05 vs. control). Elimination of buffer HCO_3 or Cl^- reduced EFS-evoked Isc. In comparison, carbachol (CCH) increased Isc by 147 ± 14 µA/cm^2 at 30 µM, an effect due to net Cl^- secretion. ATR (100nM) decreased CCH potency 211 fold; HEX or TTX did not inhibit CCH action. CCH exhibited autotachyphylaxis and this condition was produced a 70% reduction in EFS-evoked Isc. These results suggest that EFS release ACH from submucosal neurons which increases Cl^- secretion in PJ.

28.1

VITAMIN C TRANSPORT IN LIVER MEMBRANE VESICLES. J. Bianchi, H. Rambaran*, C. A. McClernan*. Deborah Research Institute, Browns Mills, NJ 08015-1799

The study was designed to elucidate the mechanism by which vitamin C is transported across the plasma membrane of the guinea pig hepatocyte. Vesiculated hepatocyte plasma membrane was chosen as the model, for metabolic artefact would be minimized. Enrichment of the membrane fraction was monitored by enzyme markers. Transmission electron microscopy showed continuous membrane vesicles. Uptake was studied by radiotracer flux using inhibitor stop and vacuum filtration techniques. Control studies included sugar transport and variation of external osmolarity. Control studies demonstrated osmotically sensitive vesicles capable of discriminating between D- and L-glucose, as indicated by initial flux rates. Uptake of L-ascorbic acid demonstrated no cation specificity as indicated by initial transport velocities with either an extravesicular to intravesicular NaCl or KCl gradient. The transport mechanism did exhibit saturation kinetics, and a linear transformation of the data provided a Km = 245±37 uM (n=6) and V = 47.8±5.7 pmol/mg protein/10 s. Isoascorbic acid is an inhibitor of L-ascorbic acid flux in this model, and given its widespread use by the food industry may be of nutritional consequence. Vitamin C is transported by a facilitated mechanism down its biochemical gradient into the liver. This work was supported by a Deborah Foundation Research Grant.

28.2

99mTc-GALACTOSYL-NEOGLYCOALBUMIN (NGA): A SUITABLE TRACER FOR INVESTIGATION OF HEPATIC FUNCTION IN LIVER CIRRHOSIS AND HEPATITIS. Christian Müller, Irene Virgolini, Peter Angelberger, Helmar Bergmann and Helmut Sinzinger. Department of Nuclear Medicine University of Vienna, Vienna, Austria.

In vitro and in vivo studies of 99mTc-NGA showed selective binding of the tracer to its specific receptor, human hepatic binding protein (HBP), a key-protein maintaining hepatic function. In a total of 150 patients with liver disease a 99mTc-NGA scintigraphy (50 nmol NGA/4mCi) was performed in order to determine hepatic function by in vivo HBP-density after calculation of hepatic blood flow. In patients with liver cirrhosis (clinical status Child A-C) the amount of HBP-receptors simulated by 99mTc-NGA-uptake in the liver was significantly ($p<0.05-0.001$) decreased compared to patients with normal hepatic function. This decrease corresponded to the clinical status of the patients: normal:0.8-1.2, liver cirrhosis A:0.6-0.8, liver cirrhosis B:0.4-0.6 and liver cirrhosis C:0.1-0.4 µmol/l. In 5 patients with acute hepatitis A or B a significant ($p<0.01-0.001$) increase of HBP-concentration was simulated by follow-up 99mTc-NGA-scintigraphies until recovery: acute phase of infection 2.9±1.5 µmol/l, after recovery 7.9±1.5 µmol/. This study offers a new way to quantify human hepatic function in vivo.

28.3

MALONDIALDEHYDE IS NOT A MARKER OF ISCHEMIA REPERFUSION INJURY IN PEDIATRIC LIVER TRANSPLANT PATIENTS. L Easterling*, AR Zucker, P Whitington*, C Broelsch*, A Nahum* and JI Sznajder. Depts. of Pediatrics, Medicine and Surgery, U of Chicago and Michael Reese Hospital, Chicago, IL, 60637.

O_2 free radicals (OFR) have been implicated in ischemia-reperfusion injury (IRI) after liver transplants. We hypothesized that malondialdehyde (MDA), a product of lipid peroxidation, would be a marker of such injury in the pediatric liver transplant patient (LTP). We obtained arterial serum samples from 10 LTP before and at 0.5, 1.5 and 48 hrs after reperfusion. The pre-op MDA values, measured fluorimetrically as the thiobarbituric acid product, were 6.81 ± 5.11 nmol/ml, similar to those of 11 age-matched patients without liver disease (5.12 ± 2.60 nmol/ml). MDA values at each post-op time were similar to pre-op values (3.81 ± 2.14, 3.50 ± 2.04, 5.52 ± 3.35 nmol/ml, respectively). In contrast, serum SGPT, an indicator of liver damage, increased from 97 ± 102 to 1,953 ± 3,503 IU during this time. While these data might signify lack of OFR participation in IRI, other possibilities are: 1. MDA is diluted by intra-op volume resuscitation; 2. MDA is removed by the lungs; 3. MDA is a poor marker of OFR effects in these patients. Supported by Child. Res. Found. and MRIC of Michael Reese Hosp.

GASTROINTESTINAL MOTILITY/NEUROBIOLOGY

29.1

LENGTH-TENSION CHARACTERISTICS & AGONIST RESPONSES OF NEWBORN RABBIT COLON. John S. Martin and James P. Ryan. Temple University School of Medicine, Philadelphia, PA. 19140

Previous work has established differences in in the contractility of adult (AD) and newborn (NB) smooth muscle (SM) from the rabbit stomach (Zitterman & Ryan, Fed. Proc. 45:1045, 1986). It is not known if such differences in contractility likewise exist in NB & AD colonic smooth muscle. **Methods.** Strips of circularly & longitudinally oriented proximal & distal colon, with mucosa removed, were prepared from 10 NB & AD New Zealand white rabbits. Length-tension (L-T) characteristics determined were active tension (A-T) & passive tension (P-T). The tensions were normalized to tissue cross-sectional area and expressed as mN/cm2. A dose response curve for Ach was generated and the Log ED50 determined.

Results:

	Prox.Circ.	Dist. Circ.	Prox. Longit.	Dist. Longit.
	A-T± S.E.			
NB	*24.8 ± 22.6	*189.5 ± 166.2	*62.9 ± 96.6	*148.7 ± 98.3
AD	1537.7 ± 668.6	2122.6 ± 960.0	637.9 ± 200.0	886.3 ± 370.3
	P-T± S.E.			
NB	83.7 ± 94.0	68.2 ± 52.5	113.6 ± 143.8	83.8 ± 74.5
AD	667.5 ± 555.7	267.5 ± 212.4	322.9 ± 226.0	99.3 ± 66.2

* $p < 0.05$

The Log ED50 for NB ranged from -4.47 to -5.58 and for AD from-5.63 to -6.14; with NB & AD proximal circular & distal longitudinal Log ED50 values being significantly different. **Conclusions.** It is concluded that; 1). NB colonic SM generates less tension than AD in response to cholinergic stimulation, 2). NB colon tended to be less sensitive to Ach than the adult and 3). elements responsible for P-T in proximal NB colon are less developed than those in distal colon, with the distal NB P-T elements approximating AD values.

Supported by NIH Grant HD 21047

29.2

EFFECTS OF AGONISTS ACTING ON NEUROTRANSMITTER RECEPTORS ON THE SMOOTH MUSCLES IN DIFFERENT REGIONS OF SHEEP STOMACH. Taher Y, El-Sharkawy* (SPON: J. Welty). Faculty of Medicine, Kuwait University, Kuwait, P.O. Box 24923 Safat, Kuwait 13110.

The effect carbachol, noradrenaline, phenylephrine, isopropylnoradrenaline (INA), ATP and vasoactive intestinal peptide (VIP) and neurotensin on the rhythmic contractile activity of sheep gastric antral smooth muscle were studied. Carbachol dose-dependently increased the force of the rhythmic contractions but at high concentrations converted them to a tonic contraction. Phenylephrine caused weak alpha receptor-mediated excitation while INA caused beta receptor-mediated inhibition. Noradrenaline exerted mixed effects. ATP, VIP and neurotensin had inhibitory effects on both muscle layers, but the effect of ATP was weaker than those of INA, neurotensin and VIP. The effects of carbachol, phenylephrine and INA were blocked by atropine, phenoxybenzamine and propranolol, respectively. This study demonstrates the existence of excitatory muscarinic receptors and inhibitory beta adrenergic, purinergic, neurotensin and VIPergic receptors on the smooth muscle cells of the sheep gastric antrum. It also points to the existence excitatory alpha adrenergic receptors the activation of which produces only weak effect. Supported by grants from Kuwait University and Kuwait Foundation for the Advancement of Science.

29.3

SPONTANEOUS CONTRACTILE PATTERNS OF THE SMOOTH MUSCLES IN DIFFERENT REGIONS OF SHEEP ABOMASAL STOMACH. Taher Y, El-Sharkawy* (SPON: J. Welty). Faculty of Medicine, Kuwait University, Kuwait, P.O. Box 24923 Safat, Kuwait 13110.

Spontaneous contractile activity was recorded from longitudinal and circular strips of the muscularis of sheep abomasum. Strips from the fundus and proximal corpus exhibited either spontaneous irregular long lasting contractions of variable durations (40 sec to 6 min) or exhibited maintained tonic contraction. Strips which showed irregular contractions responded to stretch by a progressive increase in the duration of contractions and finally ceasing to relax and generated a sustained tonic contraction. This maintained tone was shown reflect development of active tension as it was relaxed by verapamil. Strips from more distal areas (mid- and distal corpus and antrum) exhibited spontaneous phasic contractions with fixed frequencies (2-5/min) and remarkably regular duration. Muscarinic, adrenergic and histaminergic receptor antagonists had no effect on the spontaneous activity of fundic, corpus or antral smooth muscles, indicating that the spontaneous activity is probably myogenic in nature. These studies indicate that. the motility of the different regions of the abomasum of the ruminant stomach may not be very different in function or origin from those of their counterparts in the simple stomach of man and dog. (Supported by Kuwait University and Kuwait Foundation for the Advancement of Science).

29.4

CONTROL OF SMOOTH MUSCLE CONTRACTIONS DURING OBLITERATION OF ELECTRICAL CONTROL ACTIVITY. M.F. Otterson and S.K. Sarna. Medical Coll. of WI, Milwaukee, WI 53226.

Electrical Control Activity (ECA; also called slow wave) is an omnipresent oscillation of gastrointestinal smooth muscle that controls the contractility of these cells. In vivo, normal amplitude of ECA depolarization is less than the cells' excitatory threshold but, with neural or chemical excitation, depolarization amplitude exceeds the excitatory threshold and a burst of electrical response activity (ERA) occurs. A contraction is associated with each burst of ERA (spikes). We found in 12 healthy conscious dogs that administration of morphine (20, 50, 200 µg/kg i.v.) or loperamide (4 mg p.o.) obliterated ECA in the proximal small intestine in about 2 to 3 hours. In the absence of ECA, most ERA bursts and their associated contractions occurred randomly, but some migrated uninterrupted over long distances (124 ± 24 cm) at a velocity of 32 ± 7 cm/s. Normal velocity and mean distance of migration of contractions is about 4-5 cm/s and 10 to 12 cm respectively. The maximum repetition rate of contractions during ECA obliteration, 8 ± 2/min, was significantly less than normal, 18 ± 1/min. Atropine (100 µg/kg), hexamethonium (20 mg/kg), or naloxone (2 mg/kg) reversed the loss of ECA in about 15 min. We do not know precisely what happens to the resting membrane potential when ECA is obliterated. We conclude, however, that the smooth muscle may contract in the absence of normal ECA oscillations. The spatial and temporal organization of these contractions is strikingly different from normal. ECA obliteration by opioids may occur by their action at a presynaptic site because it was reversed by hexamethonium.

29.5

THE EFFECT OF δ-OPIOIDS ON POTASSIUM AND CALCIUM CURRENTS IN CIRCULAR MUSCLE FROM CAT COLON. D.R. Bielefeld* and J. Krier. Michigan State University, East Lansing, MI 48824

Whole cell patch clamp techniques were used to study membrane currents of circular smooth muscle cells dissociated from cat proximal and distal colon. A 2-3 cm segment of proximal colon 1 cm caudal to the ileocecal sphincter and a similar segment length of distal colon immediately proximal to the pelvic brim were excised. In circular muscle cells obtained from distal colon, experiments revealed two major currents: a time-independent (TI) and a time-dependent (TD) current (2-4 nA), both carried by K^+ ions. When TI and TD currents were eliminated by the presence of 20 mM TEA in the bathing solution or by K replacement by Cs in the electrode medium, a small inward Ca^{2+} current (20-50 pA) was exposed. In contrast, circular muscle from proximal colon displayed a larger inward Ca^{2+} current (50-200 pA) followed by a smaller outward TD current (1-2 nA). A non-selective µ-opioid receptor agonist, morphine ($1x10^{-5}$M), and a δ-opioid receptor-selective agonist, [D-Pen^2, D-Pen^5] enkephalin ($1x10^{-7}$M), decreased the outward TD current in both proximal and distal colon smooth muscle cells. These opioid agonists also enhanced the amplitude of the Ca current in proximal muscle; however, they had no effect on the inward current in cells from distal colon. These studies suggest that non-selective µ- and selective δ-opioid agonists mediate contraction by blockade of K conductance and enhancement of Ca conductance in circular smooth muscle of the colon. (DK-29920)

29.6

EFFECTS OF SUPERIOR MESENTERIC AND COELIAC GANGLIONECTOMY ON THE ELECTRICAL AND MECHANICAL ANTIVITY OF THE SMALL INTESTINE IN THE HANFORD MINI PIG. A.Brandl, S.B.Reiser, F.Holle, G.E.Holle Gastroenterol.Res.Lab.L.M.-Univ.8000 Munich,F.R.G.

Measurements were performed with the help of 5 bipolar serosal electrodes and 5 strain gauge force transducers (Bass et al 1969) along the small intestine before and over 6 months after ganglionectomy.Measurements before ganglionectomy served as controls. Results:BER(16.8 SW/min in duod.;12 SW/min in ileum)was unchanged after ganglionectomy. The total cycle of MMC (61.3 min.- 11) increased nonsign.Motility index(MI) in the fasted state(145 in the duodenum, 2o3 in the jejunum,122 in the ileum)increased sign.by 17%,19% and 47% respectively, due to increase in contraction frequency in phase II and an increasing duration of phase III from jejunum to ileum.In the fed state MI increased sigr by 33% in the ileum.
We attribute these findings either to the loss of extrinsic stimulation of probably inhibitory intramural neurons,or to the altered hormonal infuence of the entero-endocrine cells numerically changed through ganglionectomy(Holle et al.J.Auton.Nervous System 26(2):135-156(1989)), or to both.

29.7

MORPHOLOGICAL AND NEUROCHEMICAL PROPERTIES OF MYENTERIC PLEXUS NEURONES OF THE GUINEA-PIG DUODENUM. G.T. Pearson*, F.M. Reekie* and G.M. Lees* (SPON: J. H. Szurszewski). University of Aberdeen, Aberdeen, AB9 1AS, Scotland, U.K.

The innervation of the guinea-pig duodenum was studied by intracellular staining of myenteric plexus neurones with the fluorescent dye, Lucifer Yellow. As in previous investigations (1,2), the morphological classification of Dogiel was used as a basis for categorizing the shapes of LY-stained neurones, some of which were subsequently examined for immunoreactivity (IR) to the proenkephalin-derived peptides, Met- and Leu-enkephalin (Enk; n=126) and Met-enkephalyl-Arg-Gly-Leu (MERGL; n=35). Of the 879 neurones stained, 49% had many short soma processes and a single long process (Dogiel Type I), whereas 34% had smooth somata and several long processes (Dogiel Type II). The remaining 17% of cells could not be assigned to either of these categories. The proportions of Type I and Type II myenteric neurones in the duodenum are essentially similar to those observed in morphological studies of neurones in the ileum (3) but, by our criteria, there were greater numbers of duodenal neurones with features quite different from either of the two main categories. Enk-IR was detected in 32% of the Type I neurones studied (n=72), a proportion identical to that found in the ileum (3). In contrast, MERGL-IR was found in 68% of Type I duodenal neurones (n=25), whereas in the ileum only 36% of Type I myenteric plexus neurones show MERGL-IR (3). As in our previous studies (1,2,3), none of the Type II neurones showed Enk-IR (n=37) and MERGL-IR was confined to Type I neurones. The results suggest there may be regional differences along the alimentary tract not only in the processing of the proenkephalin precursor but also in the functions of opioid peptide-containing neurones. Electrophysiological studies of myenteric neurones of the duodenum are in progress.

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29.8

ELECTROMECHANICAL ACTIVITY FROM THE SUBMUCOSAL AND MYENTERIC CIRCULAR MUSCLE LAYERS IN THE CAT TERMINAL ANTRUM. L.M. Renzetti*, M.B. Wang, and J.P. Ryan.Dept. of Physiology, Temple Univ. School of Medicine, Philadelphia, PA 19140

Slow waves are thought to initiate contraction by reaching a membrane potential, called the mechanical threshold, required for force development. We previously have shown that significant differences in slow wave characteristics exist between myenteric (M) and submucosal (S) circular muscle (CM) in the cat terminal antrum, and that M and S layers can generate slow waves (Gastroenterology 96:A692). The present studies were designed to determine if both M and S circular muscles contract during slow wave activity. **Methods**. Muscle strips from the cat terminal antrum were pinned out in cross-section in a recording chamber perfused with Kreb's buffer (37°C) and equilibrated for 120 min. The preparation then was dissected into submucosal (0 to 25% of CM thickness) and myenteric (50 to 100% of CM thickness) segments. Approximately 1 cm of each segment was repinned, leaving a flap of muscle that was attached to a force transducer. The muscles were given an additional 60 min. equilibration. Muscle cells from M and S then were impaled with 20-40 megaohm glass microelectrodes and force and Em were recorded. **Results**. Slow waves from M consisted of an upstroke (0.22±0.04V/s), plateau and a downstroke, Em=-74±1mV, duration=5s and f=5/min, while those from S had a rapid upstroke (0.55±0.03V/s) and a downstroke, Em=-84±1mv, duration=3s and f=2/min. Contractions occurred during the upstroke of slow waves from both M and S. **Conclusions**. The data suggest: 1) Two distinct slow wave configurations exist in the CM of the cat terminal antrum: 2) M and S CM layers have pacemaking areas and generate slow waves: 3) Slow waves from M and S only reach mechanical threshold during the upstroke: 4) Electromechanical activity from M and S CM of the cat terminal antrum may occur independently of one another. Supported by NIH Grant HD21047

29.9

MEBEVERINE (MEB) - A BROAD ACTING SMOOTH MUSCLE SPASMOLYTIC DEVOID OF ANTICHOLINERGIC ACTIVITY Susan C. Pepple* & Kenneth G. Mandel. The Procter & Gamble Co., Miami Valley Laboratories, Cincinnati, OH 45239-8707.

MEB is widely used to treat functional motility disorders such as Irritable Bowel Syndrome. Since in clinical use, MEB lacks anticholinergic side-effects often seen with other spasmolytics, we wanted to compare its spasmolytic and anticholinergic activities. MEB dose-dependently inhibited contraction of guinea pig ileal longitudinal muscle induced by maximally effective concentrations of bethanechol, carbachol, CCK, histamine, 5-HT, bradykinin, substance P, NKA and NKB. Half-maximal inhibition required 1-10 uM MEB, and MEB most potently blocked responses to cholinergics and CCK. Pretreatment with tetrodotoxin failed to alter MEB's spasmolytic activity, suggesting it acted diretly on GI muscle. In other experiments, MEB failed to prevent methacholine-stimulated salivation in rats. Though salivation induced by 30 ug/Kg methacholine (iv) was completely blocked by anticholinergic pretreatment (10 ug/Kg ipratropium or 300 ug/Kg dicyclomine), 1 mg/Kg MEB (iv) had no effect. Finally, in a muscarinic receptor binding assay in which ^{3}H-QNB binding was highly sensitive to displacement by atropine and ipratropium, MEB failed to displace specificly bound QNB. These studies suggest MEB is a broad-acting spasmolytic, but lacks anticholinergic activity. Studies are in progress to elucidate whether MEB's spasmolytic activity is related to interaction with smooth muscle Ca^{++} channels.

29.10

LONGITUDINAL TISSUE IMPEDANCE IN SMOOTH MUSCLES. Anant B. Parekh*, Tadao Tomita* and Alison F.Brading*.(SPON:J.H. Szurszewski) Dept. of Pharmacology, University of Oxford.OX13QT. UK.
In smooth muscle, electrical coupling between muscle fibres is thought to play a vital role in the spread of excitation and synchronization of contractility. To obtain further information on coupling, tissue impedances of taenia, stomach (fundus, corpus, antrum), vas deferens and urinary bladder (all isolated from the guinea-pig) were studied. The impedances were measured in the frequency range 10 Hz to 20KHz, using a Gain-Phase meter (Hewlett-Packard 3575A).Preparations were held isometrically in a small horizontal plastic tube and perfused at constant rate at room temperature.The resistance of the extracellular solution was increased by isosmotically replacing NaCl with sucrose. On diluting NaCl to 70 mM, the impedance was increased and frequency-dependency became clear. The characteristic frequency of around 1 KHz corresponded to a time-constant of 0.2 mS.The low-frequency component of impedance (probably reflecting electrical coupling between cells) increased most for urinary bladder then longitudinal muscle of fundus, taenia, vas deferens, circular muscle of fundus and finally circular muscles of corpus and antrum. The high frequency component (probably a reflection of myoplasmic resistance) was between 150 and 250 ohm.cm irrespective of the muscle type. On further dilution, the high-frequency component increased by a similar amount to the low-frequency component in stomach strips suggesting an increase in a non-capacitative component. This was not observed in the taenia or vas deferens. Such a resistive component, probably arising from the extracellular space between muscle groups, ought to be included in the equivalent circuit diagram for some smooth muscles.

29.11

A DYE-COUPLING STUDY OF INTESTINAL SMOOTH MUSCLE M. Hanani* and O. Zamir*. (SPON: M. Brezis). Hadassah Univ. Hospital, Jerusalem 91240, Israel.

Gap junctions (GJs) have not been ultrastructurally observed in longitudinal smooth muscle (LM) of the small intestine. Thus, the basis for electrical coupling in LM is unclear. We injected single muscle cells in the guinea-pig small intestine with the dye Lucifer Yellow (LY) which crosses GJs. We observed dye spread among cells in both the circular muscle (CM) and LM. The mean number of coupled cells was 3.67±0.35 (N=57). Dye coupling was reduced when the intracellular pH was lowered by bubbling the bathing solution with CO2. In normal pH 85.1% of the stained cells showed dye coupling, compared with 34.8% in low pH. In the cases where coupling was observed, the number of dye-coupled cells was reduced in low pH (1.8±0.27, N=16, $p<0.0001$). Horseradish peroxidase, which does not cross GJs did not spread from injected cells. Passage of LY between LM and CM was not observed. These findings are consistent with the presence of GJs in both muscle layers and they suggest that the channels that mediate coupling in the LM are structurally different from GJs.

29.12

DOES A MECHANISM FOR SODIUM-CALCIUM EXCHANGE EXIST IN THE SMOOTH MUSCLE CELLS OF SHEEP GASTRIC ANTRUM? Taher Y, El-Sharkawy (SPON: J. Welty). Faculty of Medicine, Kuwait University, Kuwait, P.O. Box 24923 Safat, Kuwait 13110.

The purpose of this study was to investigate whether Na^{+}-Ca^{2+} exchange capable of regulating intracellular Ca^{2+} level and contractility exists in the smooth muscle cells of sheep gastric antrum. Thus, the effects of ouabain and Na^{+} poor solutions on the spontaneous rhythmic contractions of strips of this tissue were studied. Low concentrations of ouabain ($1-3x10^{-}$ M) caused a slowly developing increase in the force of the spontaneous contractions while higher concentrations caused inhibition. The introduction of sodium - poor (15.5 mM) solutions in which the NaCl was replaced by sucrose (sucrose Krebs) elicited an elevation of tone lasting several minutes. The responses to the low concentrations of ouabain and to sucrose Krebs suggest the existence of a Na^{+}-Ca^{2+} exchange mechanism in this smooth muscle which may play a role in regulating the intracellular Ca^{2+} level and contractility. This work was supported by grants from Kuwait University and Kuwait Foundation for the Advancement of Science (KFAS).

HISTORY OF PHYSIOLOGY

30.1

THE HAND, A LESSER KNOWN WORK OF SIR CHARLES BELL. Henry Brown. New England Deaconess Hosp., Boston, MA 02215 and VA Medical Center, Manchester, NH 03104.

Sir Charles Bell (1774-1842) was well known for his neurologic studies and perhaps less so for surgical and anatomical works. He not only was Professor of Surgery at Edinburgh late in life, but also wrote one of the first texts on the hand in the English language: "The Hand. Its Mechanism and Vital Endowments as Evincing Design", London, William Pickering, 1833. His comparative anatomic studies with other vertebrates are beautifully illustrated by his own drawings. His analogy of the hand to the eye in comprehending the outside world is striking. It is also prophetic, since small injuries to the eye as a small cinder in the cornea may completely incapacitate the eye just as a small nerve injury may completely incapacitate the hand. In this time of great specialization, stressing scientific instrumentation, it is inspiring to find work without such instruments, almost entirely from a fine versatile mind embellished by artistic drawing skills and unhampered by specialty boundaries.

30.2

BENJAMIN HOWARD (1836- 1900) AND THE ABC OF CARDIOPULMONARY RESUSCITATION. Robert E. Johnson and David A. Dudey*.Univ. of Vermont, Burlington, VT 05405

Everyone has cardiopulmonary resuscitation (CPR) at birth. Our first cry signals the onset of breathing. The stopping of umbilical blood flow starts circulation independent of our mother. During life CPR may be used in emergencies such as drowning, injury, or cardiac arrest. After 1840 the ABC of CPR can be based on pathophysiology. The airway must be open. Breathing can be assisted by compression alternating with relaxation, the patient being in an appropriate position.After 1910 mouth- to- mouth resuscitation was accepted, as was external cardiac massage. Benjamin Howard made two major contributions: (A) a maneuver for clearing the airway, based on his research on the epiglottis; and (B) a simple routine for thoracic compression and decompression that can be done by one operator alone for a long time without undue fatigue. Anyone using CPR now is indebted to Dr. Howard, especially those who have been revived.

40.1

INTERFEROMETRIC IMAGES REVEAL LARGE REGIONS OF CROSSBRIDGE STATIONARITY IN INTACT SKELETAL MUSCLE AT THE PLATEAU OF TETANUS. Mark Sharnoff and Hungyi Lin, Physics Dept., University of Delaware, Newark, DE 19716 (SPON: G. A. Stephens).

The steady release of heat by isometrically tetanized skeletal muscle is commonly taken to indicate that crossbridges continue to cycle even when internal shortening has ceased. Using darkfield illumination intense enough to guarantee that a typical crossbridge will scatter many quanta into the detector during each exposure, we have made double-flash holographic images of the distribution of submicroscopic motion in tetanized intact frog toe fibers during tetanus. The sensitivity of our previous methods [Biophys. J. 49 281 (1986)] has been improved, and we are now able to detect displacements as small as 1.2 nanometer in the position of any structure large enough to be resolved optically. When such a structure is nearly at rest, fluctuations in the positions of its submicroscopic components can be detected. In images made with a 25X/0.8 objective the "structures" are subsarcomeric, and the submicroscopic components to which the detector is sensitive are principally crossbridges, because the darkfield illumination has largely suppressed light scattered by the filamentary backbones. At the plateau of tetanus we find that large regions (diameter typically 100 micrometers) are effectively at rest for intervals as long as 15 msec. Our images suggest that the characteristic time for reorientation of the crossbridges in such regions is long in comparison to 15 msec.

40.2

STIMULUS-CONTRACTION COUPLING IN RAT SKELETAL MYOBALLS STUDIED BY COMPUTER VISION. V.A. Morris*, J.R. Lopez*, L. Parra*, M.L. Rolli*, and S.R. Taylor. Mayo Foundation, Rochester, MN 55905.

Myoballs are spherical, multi-nucleated, excitable, contractile cells regenerated from minced skeletal muscle. We studied them with an immersion objective, 2D CCD and computer vision system at 21 C. The system outlined features of different minimum size. Brief (1 ms) electrical stimuli induced shortening (time to peak < 40 ms) and spontaneous relaxation. Low caffeine or carbachol increased the extent and rate of shortening. High caffeine (5 mM) or carbachol (1mM) caused single contractures that were not reproducible unless a myoball was rested (about 10 min) in agonist-free solution. Hydroxy-dantrolene (EU4093) slowed or reversibly blocked contraction but solutions with no added Ca2+ and EGTA (3 mM) had no effect. EMs made after experiments aided explicit descriptions of relations among physical objects and features from computer images. Myoballs that behaved as described had randomly oriented sarcomeres in series and double hexagonal arrays of thick and thin filaments. Stimulus-contraction coupling in myoballs evidently depends on an easily depleted internal store of Ca2+. Supported by NS 22369, NSF DMB 85967345, and Angelini Pharmaceuticals, NY.

40.3

IMPROVEMENTS IN DETERMINING GEOMETRY OF LUNG PARENCHYMAL CONNECTIVE TISSUE. E.H. Oldmixon*, J. Butler*, P.-O. Forsgren*, M. Ulfsparre*, N. Åslund*, F.G. Hoppin, Jr. Brown University and Memorial Hospital, Departments of Medicine, Pawtucket, RI 02860, Biomechanics Institute and Harvard Sch. of Publ. Hlth., Boston, MA, and Physics IV, Royal Institute of Technology, Stockholm, Sweden.

Lung parenchymal tissue preserved by perfusion fixation/dehydration, stained with Lucifer Yellow CH (LYCH), and epoxy-embedded has been examined using a confocal scanning laser microscope to yield serial optical sections. These sections, when first obtained, exhibit different intensities, due to their differing depths within the sample. Two automated methods which correct a section series to uniform intensity are presented, with validation. LYCH staining emphasizes the elastin-rich connective tissue (CT) cables, which retain (we believe) their in vivo configuration. An improved method for calculating their curvature in three dimensions is presented, with validation. Three-dimensional reconstructions show both the surface and internal structures of parenchymal tissue at 0.3 μm resolution, especially the branching CT complexes at alveolar mouths. (This research is supported by NIH grants HL 26863 and HL 33009.)

ENDOTHELIUM-DEPENDENT VASOMOTOR RESPONSES

41.1

PORCINE ENDOTHELIN IS A VASODILATOR IN THE FETAL PULMONARY CIRCULATION. S. Cassin, V. Kristova*, T. Davis, P. Kadowitz, and G. Gause*. Dept. of Physiology, College of Medicine, University of Florida, Gainesville, FL 32610.

Porcine endothelin, a recently described novel polypeptide derived from cultured porcine endothelial cells, is reported to be a potent vasoconstrictor of the systemic and pulmonary circulations of adult rats, cats and dogs. The present studies were performed to test the effects of this agent on the fetal pulmonary circulation. Fetal sheep (n=15) were delivered by cesarean section from chloralose-anesthetized ewes with the umbilical circulation maintained intact. Circulation to the lower left lobe of the fetal lung was isolated in situ and perfused at constant flow (17.9+1.1 ml/kg.min) with blood from the inferior vena cava. Fetuses were prevented from breathing, thus maintaining an elevated pulmonary vascular resistance. Intrapulmonary arterial bolus injections of endothelin from 0.3 to 1000 ng, dose dependent vasodilation was observed. With 100, 300, and 1000 ng endothelin, 30, 40 and 42% decrease in PVR from control was noted. Following ventilation of the lungs with 100% oxygen (with elevation of PaO2 and decreased PVR),100 and 300 ng produced only a 5% and 9% decrease in PVR, respectively. In contrast, 1000 ng resulted in 70% increase in PVR from baseline, a complete reversal in response. Ventilation of the right lung alone (left lung in fetal state) elevated PaO2 and decreased PVR with a similar reversal in response to 1000 ng endothelin. These results demonstrate for the first time that endothelin may cause a tone dependent vasodilation in the fetal pulmonary circulation. (Supported in part by NIH Grant HL 10834).

41.2

THE VASCULAR ENDOTHELIUM DOES NOT MODIFY ENDOTHELIN CONTRACTIONS OF HUMAN ISOLATED PULMONARY VASCULAR MUSCLES. Charles Brink, Veronique Gillard*, Pierre Roubert*, Isabelle Loquet*, Pierre-Etienne Chabrier*, Pierre Braquet and Jeanne Verley*. Centre Chirurgical Marie Lannelongue, 133 av de la Résistance, Le Plessis Robinson and Institut Henri Beaufour, 1 av des Tropiques, Les Ulis, France.

Human isolated pulmonary arterial (HPA) and venous muscle preparations (HPV) obtained at surgery were cut as rings and set up in 10 ml organ baths containing Tyrode's solution at 37°C aerated with 5% CO_2 in O_2. The different types of preparations were divided into two groups, those which relaxed when challenged with acetylcholine (10 μM; R) and those which did not (NR). Endothelin concentration-effect curves were produced in all tissues using the cumulative dosing method. The pD_2 value (-log EC_{50} molar) was interpolated from each curve. The results (mean ± SEM) are presented below (N/P=number of lung samples/preparations).

Preparation		N/P	Endothelin (pD_2 value)
HPA	R	3/3	8.58 ± 0.05
	NR	3/7	8.74 ± 0.05
HPV	R	3/6	9.29 ± 0.19
	NR	4/15	9.33 ± 0.07

HPV were more sensitive to endothelin than HPA. The pD_2 values were not modified by the functional endothelium.

41.3

Methylene Blue has a direct effect on the vascular smooth muscle in the isolated perfused rat caudal artery. G. Mazmanian*, B. Baudet*, M. Weiss*, Ph. Hervé - Hopital Marie Lannelongue Le Plessis Robinson 92350 - France.

The proximal segment of the rat caudal artery (3-4 cm) was cannulated at both ends, placed in a Krebs solution at 37°C and perfused at a constant flow of 1-2 ml/mn. Responses (mmHg) to intra luminal phenylephrine (PE) were monitored before and after addition of methylene blue (MB). Intra luminal MB did not change the basal tone but markedly increased the response to PE. In contrast extra luminal MB substancially increased basal tone (+263±63 mmHg; n=5) whereas the responses to PE were unaffected. Our results suggest that in addition to its endothelium dependent effect MB may have a direct action on the vascular smooth muscle.

Response to PE after intra or extra luminal MB treatment (mmHg±SD).

INTRALUMINAL PE (M/l)	$4\ 10^{-7}$	$9\ 10^{-7}$	$3\ 10^{-6}$	$8\ 10^{-6}$	$3\ 10^{-5}$ (M/l)
CONTROLS n=5	6 ± 1.6	14.4 ± 5.9	65.6 ± 34.2	134.4 ± 72.9	201.6 ± 89.6
INTRA MB n=5	25 ± 11.8*	58 ± 21.5*	149.4 ± 40*	174.8 ± 37.5*	208.4 ± 52.2 NS
EXTRA MB n=5	4.2 ± 3.4 NS	16.2 ± 2.8 NS	67.8 ± 11.4 NS	115.2 ± 19.3 NS	164.2 ± 26.2 NS

* Significantly different from controls (p<0.05).

41.4

A MODEL SYSTEM TO MONITOR CHANGES IN LYSOPHOSPHATIDYLCHOLINE (LPC) N.K. Menon, M. Zehetgruber*, J. Pataricza*, R.J. Bing. HMRI, Pasadena, CA 91105

The availability of LPC for the endothelium-dependent relaxation of blood vessels depends on its production by deacylation of phosphatidylcholine (PC) upon various physiological stimulation. We have developed an in vitro model system to monitor changes in LPC levels. 1-^{14}C PC was incorporated into bovine intrapulmonary arterial rings by incubation in Krebs-Henseleit at 25°C for 1 hour. 50-70% of the label was incorporated. The rings were opened into strips, excess counts were washed and precontracted with 10^{-5}M histamine in the presence of 10^{-5}M indomethacin. At steady state phospholipase A_2 (2 units/ml) was added. At maximum relaxation the strips were frozen in liquid N_2. Total lipids were extracted. LPC and PC were separated by TLC and counted. The results indicate a significant increase in conversion of ^{14}C PC to LPC by exogenous PLA_2 in the presence of endothelium (P>0.01). Thimerosal which inhibits reacylation, elicited increase in LPC, while acetylcholine had no effect. This model can be applied to study the release of LPC upon stimulation with α-adrenergic agents, thrombin and shear stress.

41.5

NITRIC OXIDE AND ENDOTHELIUM. M. Zehetgruber*, J. Pataricza*, N.K. Menon, R.J. Bing. HMRI, Pasadena, CA 91105

Endothelium-derived relaxing factor may not be identical to nitric oxide (NO) (Menon et al. Proc. Soc. Exp. Biol. Med. in press). To support this conclusion, lumina of bovine pulmonary arteries with and without endothelium were incubated with Krebs-Henseleit (KH) solution at 37°C and tested for NO by chemiluminescence after purging with helium. Effluent from incubated vessels superfused precontracted endothelium-deprived artery strips. Hemoglobin (10^{-4} to 2 X 10^{-5}M) was added to the KH solution following incubation. Insignificant production of NO without acidification in intact and endothelium-deprived vessels was present. Acidification increased NO signals particularly in endothelialized vessels. Hemoglobin partially inhibited NO. Effluent from intact arteries caused relaxation despite absent NO signals. Conclusion: Incubation with KH alone produced large amounts of NO precursors. NO production without acidification is not demonstrable. Presence of endothelium increased NO production under acidic conditions. Hemoglobin partially inhibited NO production. Marked discrepancies between relaxation and NO production were present.

41.6

PURINERGIC RELAXATION AND HYPERPOLARIZATION IN THE GUINEA PIG CORONARY ARTERY: ROLE OF THE ENDOTHELIUM. K.D. Keef and S.M. Bowen*. Dept. of Physiol., Univ. of Nevada, Reno, NV, 89557.

The present study investigates the mechanism by which purinergic compounds induce relaxation in the in vitro guinea pig coronary artery. Vessels were contracted with 2-aminoethylpyridine and the dose-response relationship for relaxation with adenosine, AMP and ATP were measured and compared to 2-chloroadenosine (ClAD), 2-methylthioATP, β,γ methylene ATP and AMP-PNP. ClAD was the most potent; all other compounds were of lesser but equal potency. The dose-response relationship for ClAD was shifted to the right with 8(p-sulfophenyl)theophylline whereas relaxation with ATP was not. Endothelium removal shifted the dose-response curve for both ATP and ClAD to the right. Indomethacin (10^{-4}M) did not change the response to either ATP or ClAD whereas methylene blue (5 x 10^{-5}M) shifted the dose-response curve for both substances to the right. Spritz application of ATP, 2-methylthioATP, AMP-PNP and to a lesser extent β,γ methyleneATP led to a transient hyperpolarization of the smooth muscle cells whereas ClAD application had no effect on membrane potential. The hyperpolarization with ATP was abolished by removal of the endothelium. The results indicate that relaxation is mediated by both P_1 and P_{2y} receptors. These receptors appear to be present on both the smooth muscle cells and the endothelium. Purinergic hyperpolarization is due specifically to stimulation of P_{2y} receptors on the endothelium. Grant support HL40399.

41.7

BLOOD FLOW VELOCITY-INDUCED DILATION IN SKELETAL MUSCLE MICROCIRCULATION IN VIVO: ROLE OF ENDOTHELIUM. Akos Koller and Gabor Kaley, Department of Physiology, New York Medical College, Valhalla, New York 10595.

In cremaster muscle of pentobarbital anesthetized rats we found that temporary occlusion of a second order arteriole increased blood flow velocity (mean: 14.1±1.1 mm/sec) in proximal third order arteriolar branches (mean control diameter: 21.5±0.5μm); this flow increase was consistently followed by an increase in diameter (mean: 6.6±0.4μm). A delay (mean: 8.4±0.5 sec) was always observed between the onset of the increase of these parameters. Impairment of the endothelium of third order arteriolar segments (≈100μm long) by mercury-light/fluorescein (light/dye) technique completely blocked the response to endothelium-dependent dilator agents, acetylcholine and arachidonic acid (with no change in dilation to adenosine or sodium nitroprusside) and resulted in a slight constriction (≈2μm) to increases in flow velocity. These results suggest: 1) that the increase in blood flow velocity per se is a stimulus for arteriolar dilation and 2) that the endothelial cells are responsible for the mediation of this response. The existence of this phenomenon in the microcirculation suggests a new local regulatory mechanism which has the role of modulating vascular resistance to change blood flow distribution in microvascular networks. Supported by NHLBI Grant 37453.

41.8

INHIBITION OF ENDOTHELIN-INDUCED CONTRACTIONS BY NICKEL: PROPOSED MODEL FOR AN ADDITIONAL CALCIUM INFLUX PATHWAY K. L. Blackburn* and R. F. Highsmith. Dept. Physiology and Biophysics, Univ. of Cincinnati, Cincinnati, OH 45267

Endothelin (ET), the potent vasoactive peptide derived from endothelial cells, was originally proposed to act as an endogenous agonist for the L-type Ca^{2+} channel. Despite the requirement of ET for $[Ca^{2+}]_o$, L-type Ca^{2+} channel antagonists fail to fully inhibit ET-induced contractions. The present study evaluated the effect of $NiCl_2$ (Ni^{2+}), an inhibitor of the T-type Ca^{2+} channel in several cell types, on ET-induced contraction of porcine coronary artery (I_xAD) with intact endothelium. A 10 min. preincubation of LAD with Ni^{2+} (180 or 360 μM) followed by porcine ET (5nM), resulted in a dose-dependent reduction in maximum isometric force. Mean values at the plateau of force development +/- SEM were: 111+/-14 mN (n=19), 55+/-13 mN (n=10) and 13+/-3 mN (n=19) for the 0-, 180- and 360-μM Ni^{2+} groups, respectively. The means for both Ni^{2+}- treated groups were significantly different from the 0-Ni^{2+} control group, as well as from each other ($p < 0.01$). Similar results were obtained in deendothelialized LAD. The same concentrations of Ni^{2+} had negligible effects on contractions induced by KCl (77mM) or by the L-type Ca^{2+} agonist, (+)-S202-791 (1μM). In preliminary experiments, membrane depolarization by KCl (5-10 mM) partially ameliorated the inhibitory effect of Ni^{2+}. These data support a sequential mechanism of action in porcine LAD whereby ET must first activate a Ni^{2+} sensitive process, perhaps the T-type Ca^{2+} channel, prior to the indirect activation of the L-type Ca^{2+} channel. (Supported in part by NIH HL 31543).

42.1

CENTRAL NERVOUS EFFECTS OF TACHYKININS ON TRACHEAL SUBMUCOSAL GLAND SECRETION. M.A. Haxhiu, E. van Lunteren, N.S. Cherniack. Case Western Reserve University, Cleveland, OH 44106

The purpose of this study was to assess the importance of tachykinins on the central regulation of glandular secretion. We examined the changes in secretion from single submucosal glands in an exposed section of tracheal epithelium (1.2 cm^2) coated with tantalum dust, before and after intracisternal injection of SP, NKA and NKB, and topical application of SP and NKA on the intermediate area of the VMS. Experiments were performed in chloralose anesthetized dogs, artificially ventilated with 100% O_2. Following a 60 s baseline period, we infused, intracisternally, 0.25 ml of buffered saline or tachykinins (SP: 4 dogs; NKA: 2 dogs; NKB: 1 dog) in doses of 10^{-6} - 10^{-4}M for 15 s, and counted hillocks appearing in subsequent one and two minute intervals. In another series of experiments, pledgets containing SP (5 dogs) and NKA (1 dog) were applied topically to the VMS (10^{-6} - 10^{-3}M). The number of glands producing hillocks (>0.2 mm dia) after intracisternal tachykinin infusion was significantly higher than following administration of buffered saline (43.6 ± 3.5 vs. 10.7 ± 1.6; $p<0.01$; mean ± SE). Topical application of SP and NKA to the VMS also stimulated tracheal submucosal gland secretion; the number of activated glands increased from 13.3 ± 3.1 in the control period to 38.7 ± 10.4 after applying tachykinins to the VMS ($p<0.05$). Intravenous administration of atropine prevented the secretory changes induced by the central action of tachykinins. In addition, prior application of 2% lidocaine blocked the responses caused by tachykinins applied topically to the VMS. These findings suggest that activation of tachykinin receptors on the brainstem, including structures near the VMS, increases submucosal gland secretion in dogs via cholinergic mechanisms. SUPPORTED BY: HL-01600, HL-38701 and HL-25830

42.2

Muscarinic receptors involved in mucus secretion and increased short circuit current (I_{sc}) in swine trachea. Jerry M. Farley and Terry M. Dwyer. Dept. of Pharm. and Toxicol., Dept. of Physiol. and Biophys. Univ. of Miss. Med. Ctr., Jackson, MS 39216

Mucus is secreted from tracheal submucosal gland cells following parasympathetic nerve stimulation. The mucus then takes up additional water in order to reduce its viscosity. This study examines the correlation of mucus secretion and processes which may be involved in water transport in swine tracheal epithelium. Mucus glycoprotein secretion was measured in explants of epithelium preincubated in [^{3}H] glucosamine. Short circuit current was measured using Ussing chambers. Acetylcholine (ACh) induces a dose-dependent increase in mucus secretion with an $ED_{50} < 10^{-6}$M. Mucus secretion is transient lasting 15 min during continuous ACh challenge. After washing out ACh, reapplying an equal ACh dose induces an equal amount of release. Pirenzepine (PZP), an M_1 selective antagonist, shifts the dose response curve for ACh at high PZP concentrations (~1mM) suggesting the involvement of M_3 receptors in secretion. Short circuit current is also increased by ACh in a dose-dependent fashion with an $ED_{50} < 10^{-6}$M. The maximal change in I_{sc} induced is ~20mA (1.26 cm^2). The dose-response curve is shifted by PZP; the calculated K_I using the dose-ratio method is ~60nM. Previously, we have shown that M_1 and M_3 receptors exist in submucosal gland cells with K_I's for PZP of 10nM and 250 nM respectively. Thus mucus secretion is mediated predominantly by M_3 receptors and the increase in I_{sc} by M_1 receptors. (Supported by the MS Lung Association and NIDA grant 05094)

42.3

PERFUSED BRONCHIAL PREPARATION FOR MEASUREMENT OF MUCUS SECRETION. *Ralph J. Altiere and David C. Thompson.* University of Colorado School of Pharmacy, Boulder, CO 80309-0297

A preparation was developed for the measurement of mucus secretion in intrapulmonary airways. A 15 to 20 mm section of lobar bronchus with all bronchial branches ligated was removed from the right and left lung lobes of male ferrets and cannulated at both ends. The preparation was transferred to an organ bath containing M-199 supplemented with antibiotics, aerated with 95%O_2-5%CO_2 at 37°C and was connected to a perfusion apparatus from which perfusion pressure was monitored continuously. Following a 30 min wash-out period, the tissue was incubated with ^{3}H-glucosamine for 16 hrs. After an initial 1 hr wash-out period, secretion of ^{3}H-labeled mucus glycoproteins into the perfusate was determined by ethanol precipitation and filtration. Basal secretion rate was determined for 30 min. Thereafter, the tissue was challenged with 1 µM methacholine (MCh), the perfusate collected every 5 min for 30 min, the content of ^{3}H-labeled mucus determined and the tissue washed for 30 min. This protocol was repeated 3 additional times. Mucus secretion was maximal after the first MCh challenge and stabilized to a lower level during subsequent MCh challenges. Mucus secretion was insensitive to indomethacin treatment but was inhibited by atropine. The rise in perfusion pressure induced by MCh was blocked by atropine and enhanced by indomethacin pretreatment. Histological examination of bronchial segments confirmed that epithelium remained intact throughout the experimental procedures indicating that little or no damage resulted from tissue perfusion. The results indicate that the perfused bronchial preparation is a suitable model for examining the regulation of mucus secretion in small intrapulmonary airways. *DCT is a Parker B. Francis Fellow in Pulmonary Research. Supported by a grant from the Cystic Fibrosis Foundation.*

42.4

PAF-INDUCED HYPERRESPONSIVENESS OF FERRET TRACHEAL SMOOTH MUSCLE AND MUCUS SECRETION IN VITRO. S.E.Webber* and J.G. Widdicombe, Dept of Physiology, St George's Hosp Med School, London SW17 ORE, UK.

Whole ferret tracheas were mounted air-filled in organ baths at 37°C, with abluminal Krebs-Henseleit buffer containing 4mg.ml^{-1} bovine serum albumin (BSA) and 30µg.ml^{-1} fluorescent BSA. Secretions were collected and mucus volume, lysozyme and albumin outputs determined. Intraluminal pressure (tracheal smooth muscle tone) and potential difference (PD) across the epithelium were measured. Concentration-response curves for methacholine were determined before and after a 2-h abluminal exposure to PAF (1µM). PAF did not change mucus volume, lysozyme and albumin output. It relaxed the trachea (-32 ± 6 mm H_2O) and reduced PD from 7.1 ± 1.3 to 3.0 ± 0.3 mV (n=8). Results for methacholine were (means, $p<0.05$):

	EC_{50} (µM)		Maximum response	
	Before PAF	After PAF	Before PAF	After PAF
Pressure	2.2	0.6*	126	162* mm H_2O
Mucus	1.6	0.8*	1.64	2.44* µl.min^{-1}
Lysozyme	2.1	1.2*	0.37	0.58* µg.min^{-1}
Albumin	0.9	0.9	2.62	1.30* µg.min^{-1}

Thus PAF produces hyperresponsiveness of tracheal smooth muscle and submucosal gland secretion to methacholine in the absence of platelets. The decrease in PD and methacholine-induced albumin transport after PAF suggest loss of epithelial function.

AIRWAY SMOOTH MUSCLE

43.1

CHOLINERGIC REACTIVITY OF TRACHEAL SMOOTH MUSCLE FOLLOWING INFECTION WITH FELINE HERPESVIRUS-I. C.R. Killingsworth, N.E. Robinson, C. Berney*, T. Adams, and R.K. Maes*, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824-1314.

Cats were exposed orally, nasally, and conjunctivally to an upper airway epitheliotropic virus (1 ml of 10^6 TCID50 of C27 strain of feline herpesvirus-I; n=15) or sham-infected (n=12). Anesthetized cats were studied on post-inoculation day (PID) 3 or 6. Tracheal smooth muscle shortening was quantitated by means of a microfoil strain gauge device which measured the external diameter of tracheal ring 4 (TR4). Intrathoracic airways were evaluated by pulmonary resistance (R_L) and dynamic compliance (Cdyn). Smooth muscle contraction was produced using bilateral stimulation of the distal ends of the cut vagus nerves (24 V, 0.5 ms, 0.5-16 Hz) and increasing concentrations of acetylcholine (ACh) infused locally into the trachea via the cranial thyroid artery. There was no significant difference in the mean base-line outer diameter of TR4 in control and infected cats (0.89±0.02 cm; 0.93±0.03 cm, respectively). The diameter of TR4 decreased as the frequency of vagal stimulation increased and at 4, 8, 12, and 16 Hz there was more narrowing in infected cats at PID3 than in either PID6 or control cats ($P<0.05$). A difference of responsiveness to locally infused ACh was not observed. Atropine (2mg/kg iv) blocked the response to both ACh and vagal stimulation. R_L increased with increasing stimulus frequency and C_{dyn} tended to decrease, but there was no difference in control and infected cats. R_L and C_{dyn} were unaffected by intra-arterial ACh. Herpesvirus causes increased responsiveness to vagal stimulation in the trachea but not intrathoracic airways. The lack of increased tracheal response to local ACh suggests that the vagal effects at PID3 are presynaptic. (HL01900)

43.2

ISOPROTERENOL AND ELECTRICALLY STIMULATED RELAXATION OF AIRWAYS FROM HORSES WITH RECURRENT OBSTRUCTIVE PULMONARY DISEASE. N.E. Robinson, R.V. Broadstone, P.H. LeBlanc, F.J. Derksen. Pulmonary Laboratory, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824.

To characterize the relaxation of airway smooth muscle in horses with recurrent airway obstruction (heaves), trachealis muscle strips (TR) and third generation bronchial rings (3B) with epithelium intact of 5 normal and 5 diseased horses were compared. Tissues were pretreated with indomethacin (3 x 10^{-6}M) and precontracted with histamine to approximately 60% of the active tension achieved with acetylcholine (10^{-3}M). The precontracted tissues of both groups demonstrated a concentration-dependent decrease in active isometric tension in response to cumulative 1/2 log doses (10^{-10}-10^{-4}M) of isoproterenol (ISO). All tissues relaxed to baseline (100%). The EC_{50} values at each level of airway were not significantly different between the diseased and normal animals. Transmural electrical stimulation (ES) (18 v, .5 ms, 5-32 Hz) of precontracted TR and 3B pretreated with 10^{-6}M atropine (ATR) + 10^{-6}M phentolamine caused relaxation of 80-90% in the TR, which did not differ between groups. The 3B normal airways relaxed 19% and the 3B of diseased airways did not relax in response to ES. ES of TR and 3B pretreated with ATR, 10^{-6}M phentolamine, and 10^{-6}M propranolol caused relaxation of 46% in the normal and diseased TR and 13% in the normal 3B. Following 3 x 10^{-6}M tetrodotoxin, no relaxation was seen in the TR and 3B. This suggests no difference in the sympathetic and nonadrenergic inhibitory innervation of the equine trachea in the normal and diseased airways. However, unlike normal 3B airways, the diseased 3B airways do not relax in response to ES. (HL27619, HL01742, Boehringer Ingelheim Animal Health)

43.3

IN VITRO RESPONSES TO ACETYLCHOLINE AND ELECTRICAL STIMULATION OF AIRWAYS FROM HORSES WITH RECURRENT OBSTRUCTIVE PULMONARY DISEASE. R.V. Broadstone, P.H. LeBlanc, F.J. Derksen, N.E. Robinson. Pulmonary Laboratory, College of Veterinary Medicine, Michigan State University, East Lansing, MI.

Horses with recurrent airway obstruction (heaves) demonstrate increased airway responsiveness to various stimuli during acute exacerbations of airway obstruction (*J. Appl. Physiol.* 58: 598, 1985). To determine the possible contribution of an abnormal sensitivity of airway smooth muscle in these animals, the in vitro contractile responses to cumulative doses (10^{-9}-10^{-3}M) of acetylcholine (ACH) in strips of trachealis muscle (TR) and third-generation bronchial rings (3B) with intact epithelium of 5 normal and 5 diseased equine airways were compared. ACH produced a smaller maximal active tension per gram of tissue in the TR and 3B in the diseased tissues. Transmural electrical stimulation (ES) of 5 normal and 5 diseased equine airways of the TR and 3B through a range of voltages (6, 9, 12, 15, 18, and 20) and frequencies (1, 3, 5, 10, 15, 20, 25, and 32 Hz) at 0.5 ms showed that the diseased TR compared to normals were hyperresponsive to ES on a g/g basis, especially at lower voltages and frequencies. The diseased 3B were hyperresponsive (g/g) only at 6 volts and hyporesponsive at higher voltages. However, in comparing the ES of TR and 3B to %ACH maximum, both diseased TR and 3B demonstrated hyperresponsiveness compared to the normal airways. Atropine and tetrodotoxin eliminated the smooth muscle contractions to ACH and ES, demonstrating the presence of cholinergic excitatory nerves. We conclude that, in vitro, smooth muscle of diseased horses is hyporesponsive to ACH, suggesting that the in vivo hyperresponsiveness is not related to a primary abnormality of airway smooth muscle. The hyperresponsiveness to ES is consistent with in vivo data demonstrating a large cholinergic component of airway obstruction in this disease. (HL27619, HL01742)

43.4

THE RELATIONSHIP BETWEEN AIRWAY RESPONSIVENESS AND THE QUANTITY OF AIRWAY SMOOTH MUSCLE (ASM) IN THE GUINEA PIG. **A.M.Opazo-Saez*, T. Dut, N.S. Wang, J.G. Martin. Meakins-Christie Laboratories, McGill Univeristy, Montreal, Quebec, H2X 2P2, Canada.**

The purpose of the study was to see if the quantity of ASM was related to maximal methacholine (MCh) induced bronchoconstriction. To do this, we performed MCh concentration-response curves in 5 guinea pigs anesthetized with urethane (1.5 g/kg i.p.), paralyzed (pancuronium bromide 0.1 mg/kg, i.v.) and mechanically ventilated. Immediately after the maximal response (Rmax) was achieved, animals were exanguinated and the lungs were fixed with 10% formalin at a pressure of 25 cmH_2O. Extraparenchymal (E) and intraparenchymal (I) airways were studied (n=216). For each airway, the area of smooth muscle (SM) and the length of BM (LBM) were determined. Intraobserver variability was less than 2%. ASM was corrected for the airway size by dividing by LBM^2. There was a marked decrease in ASM/LBM^2 with increasing airway size, with a more than 10-fold difference in the amount of ASM between the smallest and the largest airways. Rmax showed a 2.7 fold range in variability. There was no correlation between Rmax and ASM for I whose LBM < 1250 u, LBM > 1250 u, or the extraparenchymal airways. We conclude that the quantity of ASM does not determine differences in Rmax among normal guinea pigs. (Supported by M.R.C. Canada.)

43.5

A COMPARISON OF CANINE TRACHEALIS MUSCLE SHORTENING IN VIVO AND IN VITRO. M. Okazawa, K. Ishida, P.D. Pare, S. Osborne, R.R. Schellenberg, J. Road, UBC Pulmonary Research Laboratory, St. Paul's Hospital, Health Sciences Centre Hospital, Vancouver, B.C. Canada V6Z 1Y6.

Maximal trachealis muscle shortening (TMS) in vivo is less than the maximal shortening in vitro during isotonic contraction from optimal length (Lmax). TMS in vivo may be limited by the elastic recoil of the cartilage which increases with muscle shortening. To quantitate the effect of an elastic load on the trachealis, we compared TMS in vivo and in vitro in 7 dogs. In vivo we measured TMS in response to maximal vagal stimulation using sonomicrometry. The muscle strip adjacent to the in vivo strip was excised and its response at Lmax with linear elastic load (0.5 - 50 g/cm) was measured. The elastic load corresponding to the measured in vivo shortening was estimated by interpolation from the relationship between elastic load and the shortening in vitro. Maximal shortening in vivo was 28.8 ± 11.7 % of initial length. The maximal isotonic shortening in vitro was 68.4 ± 3.5% at Lmax. The relationship between elastic load and active shortening was hyperbolic. The estimated elastic load standardized by contractile ability using maximal isometric tension at Lmax (Pmax) was 1.8 + 1.4 g/cm/Pmax. We conclude that relatively small elastic loads provided by the cartilage can explain the reduced shortening of canine trachealis muscle in vivo.

43.6

M_3 MUSCARINIC RECEPTOR SUBTYPE MEDIATES THE RESPONSE OF CANINE TRACHEAL SMOOTH MUSCLE STRIPS TO ACETYLCHOLINE. J.-F. Brichant*, D.O. Warner*, S.J. Gunst, K. Rehder. Departments of Anesthesiology, Physiology and Biophysics and Internal Medicine, Mayo Clinic and Foundation, Rochester, MN 55905.

Muscarinic receptors on the smooth muscle cell membrane mediate the contractile response of airway smooth muscle to acetylcholine (ACh). Currently, muscarinic receptors can be functionally subtyped into M_1, M_2, M_3 receptors according to their affinity for the antagonists pirenzepine (PZP), gallamine (GAL) and 4-diphenyl-acetoxy-N-methylpiperidine (DAMP) (Am. Rev. Respir. Dis. 138:765, 1988). To determine which muscarinic receptor subtype mediates cholinergic neurotransmission at the airway smooth muscle membrane level, we compared in vitro contractile responses of canine tracheal smooth muscle strips to ACh (10^{-8} to 10^{-3}M) in the absence and in the presence of either PZP (10^{-8} to 10^{-5}M), GAL (10^{-7} to $10^{-4.5}$M) or DAMP (10^{-10} to 10^{-5}M) while propranolol and hexamethonium were present in the tissue bath solution. GAL (n=6) had no statistically significant effect on contractile responses to ACh. All concentrations of DAMP (n=6) and concentrations of PZP $\geq 10^{-7}$M (n = 6) inhibited contractile responses to ACh. The pA_2 values were (mean ± SD) 8.99±0.16 and 6.77±0.25 for DAMP and PZP respectively. These pA_2 values are consistent with an activation by ACh of an homogeneous population of M_3 receptors in canine tracheal smooth muscles. (Supported by grants HL 21584, HL 29289 and GM/HL 40909.)

43.7

ROLE OF ANTIGEN AND EPITHELIUM ON EQUINE AIRWAY SMOOTH MUSCLE CONTRACTILITY. G.J. Tessier*, S.M. O'Grady and M.S. Kannan*, Dept. of Vet. Biol., University of Minnesota, St. Paul, MN 55108.

The mechanism of Aspergillus fumigatus antigen-induced contraction (Ag), and the role of epithelium in the modulation of contractile responses to electrical field stimulation (EFS), acetylcholine (Ach), and KCl were studied in vitro in strips of equine tracheal smooth muscle (TSM). Isometric tension was measured in strips bathed in Kreb's solution at 37°C, bubbled with 95% O_2/5% CO_2. In TSM isolated from naturally sensitized ponies, Ag and leukotriene C4 and D4 (LT) elicited dose-dependent contractions, reversible by the LT receptor antagonist FPL 55712 (1 µg/ml). EFS with .5 ms pulses of optimum voltage resulted in frequency dependent and tetrodotoxin (TTX) sensitive contractions of TSM. Removal of epithelium as well as preincubation with 1-5 µM indomethacin (I) significantly potentiated their responses, especially at lower frequencies. Ach and KCl dose-response curves were shifted to the left by removal of epithelium, with no further effects seen with addition of I. These results suggest: a) evidence of LT release by Ag in sensitized TSM, b) an epithelial-derived inhibitory factor that modulates contractility in a non-specific manner, and c) an inhibitory prostaglandin that appears to modulate Ach release from nerves.
(Supported by: U. of M Graduate School and 3M Company)

43.8

INHIBITION OF AIRWAY RESPONSES TO ENDOTHELIN-1 BY MECLOFENAMATE. Maynard Dyson, Robert Beckerman, and Philip Kadowitz*, Tulane Medical School, New Orleans, LA. 70112. Supported in part by NIH Grants HL07879, HL15580, and a grant from the American Heart Association.

The pulmonary effects of endothelin-1 (ET-1) and their blockade by meclofenamate (MEC) were studied in anesthetized mechanically ventilated cats. Transpulmonary pressure (Ptp), lung resistance (R), dynamic compliance (Cdyn), and aortic pressure (Pao) were recorded. ET-1, 0.1 and 0.3 nmol/kg i.v. increased R and Ptp and decreased Cdyn. Pao initially decreased and then increased in a dose dependent manner. MEC a cyclooxygenase inhibitor, 5 mg/kg i.v. administered before ET-1 significantly reduced the changes in Ptp, R, and Cdyn but not Pao in response to the peptide. Arachidonic acid was administered as a control to show blockade by MEC.

Response to Endothelin-1 (.3nmol/kg)

	Control (N=9)	After Meclofenamate (N=5)
Ptp (cm H_2O)	.87 ± .16	.22 ± .10
R (cm H_2/sec)	2.63 ± .50	.4 ± .25
Cdyn (ml/cm H_2O)	-.78 ± .11	-.32 ± .06
Pao (mm Hg)	-23.11 ± 3.76	-34 ± 5.57
	39 ± 2.4	52 ± 14.37

All responses to arachidonic acid were inhibited in the MEC treated cats. These data suggest that the airway responses but not the cardiovascular effects of ET-1 are mediated in part by the release of cyclooxygenase products.

43.9

Amiloride Potentiates the Acetylcholine induced contraction of rat tracheal smooth muscle. Guido E. Santacana. Dept. of Physiology UCCEM School of Medicine, Cayey, Puerto Rico.

Amiloride (*A*), the well known potassium sparing diuretic, has been shown to induce relaxation of canine tracheal smooth (CTM) muscle during carbachol (CCh) induced contraction. This effect of *A* has been adscribed to the inhibitory action of this drug on the Na^+/H^+ exchange mechanism in CTM. In addition it has also been observed that pretreatment with *A* significantly reduces the acetylcholine (Ach) induced contraction of rat tracheal smooth muscle (RTM). In this case the effect has been related to an action of *A* on the muscarinic receptor of RTM.

Experiments performed in our laboratory have shown that during Ach induced contraction *A* (20 μM - 10^{-3} M) produces potentiation effect in RTM. This effect is not observed during maximal RTM contraction induced by Ach. Furthermore a reduction of the pH (7.4-6.2) in the incubation medium simultaneous with the application of *A* will reverse the potentiation elicited by this drug on the Ach-induced contraction. The effect of the lower pH on the Ach-induced contraction can be observed in the absence and presence of *A* suggesting that it may be mainly related to an inhibitory effect on the Na^+/H^+ exchange mechanism and not directly related to the potentiation elicited by *A*.

The results suggest that during the Ach induced contraction of RTM, *A* may act by an effect that is not related to the Na^+/H^+ exchange mechanism but may be described as an action of this drug upon mechanisms that mediate the transduction of information related to the effect of Ach in the smooth muscle cells.

43.10

EPITHELIAL DEPENDENCE OF TRACHEAL SMOOTH MUSCLE CONTRACTION ELICITED BY ENDOTHELIN IN GUINEA PIGS IN VIVO. S. R. White, D. P. Hathaway*, J. G. Umans, and A. R. Leff. U. of Chicago, Chicago, IL 60637

We studied the effect of epithelial mediation of tracheal smooth muscle (TSM) contraction to endothelin (EN) in 26 male Hartley guinea pigs (GP) *in vivo*. Segments of mid-cervical trachea were isolated and tethered to a force transducer for isometric measurement of active tension (AT) in tracheal smooth muscle (TSM). Lung resistance (R_L) was measured simultaneously. All GP had bilateral vagotomy; agonists were administered iv through a jugular venous catheter. Topical EN (100 ng) applied to tracheal epithelium (EP) in 4 GP caused AT beginning < 2 min; maximal AT of 2.70 ± 0.24 g/cm was achieved after 25 min ($P < 0.01$ vs baseline). Contraction caused by 100 ng topical EN in 3 GP persisted > 3 hr. EN did not alter contraction to 3 x 10^{-7} moles/kg iv ACh administered 30 min after application (0.70 ± 0.19 g/cm) compared to baseline (0.65 ± 0.11 g/cm). Removal of the overlying EP in 3 GP augmented maximum AT elicited by topical EN (4.63 ± 0.73 g/cm, $P < 0.05$ vs intact EP). Intravenous EN (100 nmole/kg) in 5 GP elicited a *biphasic* response: initial relaxation (-0.46 ± 0.29 g/cm after 1 min), followed by sustained contraction (1.75 ± 0.32 g/cm after 7 min) and substantial increase in R_L (0.13 ± 0.03 to 1.09 ± 0.31 cm H_2O/ ml/s). Epithelial removal in 5 GP decreased significantly late contraction (0.49 ± 0.15 g/cm, $P < 0.01$ vs EP intact) but not early relaxation (-0.27 ± 0.33 g/cm) to iv EN. Pretreatment with 20 mg/kg indomethacin abolished TSM contraction and increases in R_L. We demonstrate that EN elicits airway contraction in GP by a mechanism that is partially EP dependent. Contraction of TSM elicited by EN is attenuated by epithelial removal and abolished by inhibition of cyclooxygenase [Support: HL 32495, HL 35718 and a grant from the ALA].

43.11

EFFECT OF ISOPROTERENOL ON BRONCHIAL AND VASCULAR SMOOTH MUSCLE IN RATS. P Di Blasi*, N De Marzo*, A Di Stefano*, M Saetta*, I Calliari*, LM Fabbri. University of Padua, Italy.

We investigated the effect of chronic administration of isoproterenol on smooth muscle thickness and myosin content in bronchi and pulmonary arteries of rat lungs. We administered isoproterenol (0.2 mg/kg) to 5 Wistar rats, and olive oil vehicle to 5 control rats, subcutaneously once a day for two weeks. The bronchi and the accompanying pulmonary arteries were dissected as much peripherally as possible. The proteins were extracted and loaded on 10% SDS-PAGE. Myosin content was determined by mean of Image Analyzer IBAS 2000. Controlateral bronchi and accompanying pulmonary arteries were examined by light microscopy in order to quantify the smooth muscle thickness. In bronchi, but not in pulmonary arteries, muscle thickness and myosin content were significantly reduced in treated rats compared to controls (mean±SEM).

	Myosin Content (ug/100 mg tissue)		Smooth Muscle Thickness (% Diameter)	
	Bronchi	Arteries	Bronchi	Arteries
Treated	*99±20	144±30	*8±2	24±2
Controls	218±29	217±74	13±2	28±3

These results suggest that chronic administration of isoproterenol reduces the amount of smooth muscle and contractile proteins in rat bronchi but not in the accompanying pulmonary arteries.

43.12

CHOLINERGIC POTENTIATION OF SPONTANEOUS ELECTROMECHANICAL ACTIVITY IN HUMAN FETAL AIRWAY SMOOTH MUSCLE. LS. Richards* (SPON: S.M. Brooks). College of Public Health, Univ. South Florida, Tampa, FL 33612.

Although the electromechanical properties of, and the cholinergic innervation to adult airway smooth muscle (ASM) has been extensively studied, there is little information available on the electromechanical properties of developing human ASM, and the role of cholinergic mechanisms in regulating bronchomotor tone. Fetal tracheae were obtained at the time of elective abortion, and transported to the laboratory within 30 minutes in oxygenated and cold physiological salt solution (PSS). A total of 5 tracheae obtained between 12-16 weeks of gestational development were used. Each trachea was dissected, and a portion of trachealis muscle weighing approximately 8 mg wet weight was pinned, luminal side up in a specially constructed Sylgard-coated, 2 ml plexiglass perfusion chamber. Muscle tension, and transmembrane potentials were measured simultaneously using an isometric force transducer and a standard 3 M potassium chloride-filled glass microelectrode with a tip resistance between 40-60 MΩ. Preparations were continuously superfused with fresh PSS oxygenated with 95% O_2 / 5% CO_2 (pH = 7.4) at 37°C. Preparations were stimulated with an electronic stimulator and stimulus isolation unit using single constant current pulses which were 1 msec in duration, 2.0 times threshold intensity, and delivered across bipolar platinum electrodes located on either side of the preparation. All preparations showed spontaneous phasic electromechanical activity. The maximum diastolic potential was approximately -56 mV, with slow-wave oscillations in membrane potential and tension. The amplitude of electrical oscillations was approximately 5 mV, and could be increased using electrical field stimulation. This was accompanied by a corresponding increase in muscle tension. Atropine (10^{-7} M) abolished this potentiation, but had no apparent effect on the slow-wave oscillations of electromechanical activity. Slow-wave activity was, however, completely suppressed in the absence of extracellular Ca^{++}, thereby suggesting the importance of this ion in maintaining spontaneous electrical oscillations which may contribute to bronchomotor tone *in utero*.

43.13

EXCITATION-CONTRACTION COUPLING IN TRACHEAL SMOOTH MUSCLE STUDIED WITH SPECIFIC INHIBITORS OF Na^+ CHANNEL AND Na^+-H^+ ANTIPORTER. R. Bose, J. Yu* and E.J. Cragoe* (Spon: D. Bose). Dept. of Pharmacology, Univ. of Manitoba, Canada and 2211 Oak Terrace Drive, Lansdale, Pennsylvania 19446, USA.

Canine tracheal smooth muscle contracted with carbachol can be made to relax with amiloride (J.P.E.T. 284: 408-412, 1988). Two rates of relaxation are observed suggesting two modes of action. Most of the known actions of amiloride on intact tissue appear to require Na^+. Although the role of Na^+ is not understood in smooth muscle E-C coupling, it appears to play an important role since the rate of tension development is only a tenth in absence of Na^+ when compared to controls. Phenamil, a specific inhibitor of the Na^+ channel, and 5(n-methyl n-guanidino carbonyl methyl) amiloride (GCMA), a specific inhibitor of the Na^+-H^+ antiporter were used to further evaluate the role of Na^+ in smooth muscle contraction. GCMA relaxed the muscle strips only in the presence of Na^+. The relaxation was preceded by a drop in cytosolic pH as measured with fluorescent probe BCECF. Phenamil, on the other hand relaxed the tracheal strips without any drop in cytosolic pH. Two components in the rates of relaxation were observed in the presence of Na^+ and only one in its absence (n-methyl glucamine substituted for Na^+). Calcium or barium induced tension development in Na^+ and Ca^{2+} free medium was also blocked by Phenamil, suggesting effects on the calcium channel. Thus the E-C coupling in tracheal smooth muscle requires both Na^+ and Ca^{2+} in the extracellular medium.

43.14

MECHANISM OF AZELASTINE INHIBITION OF TRACHEAL SMOOTH MUSCLE CONTRACTION IN GUINEA PIG. H.K. Lee, Y. Ohya' and N. Sperelakis. Dept. of Physiology & Biophysics, Univ. of Cincinnati, Cincinnati, OH 45267-576

Azelastine, [4-(p-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1-(2H)-phthalazinone hydrochloride], is a newly available anti-asthmatic drug. We examined the mechanisms of its inhibitory action on guinea pig tracheal muscle contraction measuring membrane potential and isometric force using intracellular microelectrodes and a micro-force transducer. Some guinea pig tracheal muscles had phasic electrical and mechanical activity, whereas other muscles were quiescent. The mean resting potential was -54±1 mV. Tetraethylammonium (20 mM) caused membrane depolarization and elicited spontaneous Ca^{2+} dependent action potentials. Azelastine (1-100 μM) supressed both amplitude and maximal rate of rise of the action potentials. Complete abolition occurred at 100 μM. Similarly, azelastine (0.1-100 μM) inhibited and abolished 50 mM KCl-induced contractions. Pretreatment of the muscles for 15 min with azelastine (0.01-100 μM) inhibited the subsequent acetylcholine (ACh) (0.01-100 μM)-induced contraction in a concentration-dependent manner. 100 μM azelastine completely abolished the ACh-induced contraction, whereas the Ca^{2+} channel blocker, diltiazem (10-100 μM) only partially depressed the contraction, suggesting an additional intracellular effect of azelastine. In Ca^{2+}-free solution (containing 0.5 mM EGTA), azelastine (1-100 μM) depressed and abolished the phasic contractions induced by 10 μM ACh. We conclude that azelastine inhibits bronchoconstriction by affecting voltage-sensitive Ca^{2+} slow channels on the cell membrane and possibly Ca^{2+} release from the intracellular store site. This study was supported by Wallace Laboratories.

43.15

DOSE-DEPENDENCE OF ACh-INDUCED CHANGES IN INTRACELLULAR Ca^{+2} CONCENTRATION AND TENSION IN TRACHEAL SMOOTH MUSCLE. C. C. Shieh., M. Petrini[1], T. M. Dwyer[2], and Jerry M. Farley, Dept. Pharm. & Tox., Dept. Med.[1] and Dept. Physiol.[2], Univ. of MS. Med. Ctr., Jackson, MS 39216.

Simultaneous measurement of intracellular calcium concentration and acetylcholine-induced isometric tension in swine tracheal smooth muscle were performed. Tracheal smooth muscle strips were loaded with Fura2/AM (8 μM) for 8-12 hours at 37°C, mounted vertically in an Aminco SPF-500C spectrofluorometer and hooked to force transducer with fine silk thread. The ratiometric method of measuring changes in intracellular free calcium concentration was used. ACh (1×10^{-7} M) gradually increased calcium concentration to 158.8 ± 15.5 (nM) above resting levels after 5 minutes. At this ACh concentration tension was 15.1 ± 4.5% of maximum. The time course of contraction mirrored the change in calcium concentration. However, with higher doses of ACh, a transient peak increase in calcium concentration was induced within 40 seconds of ACh addition to 331.1 ± 37.4 nM, 436.1 ± 64.5 nM, and 435.4 ± 71.1 nM (10^{-6} M, 10^{-5} M, and 10^{-4} M, respectively). Free calcium then declined after 5 minutes to plateau concentrations of 254.7 ± 28.4 nM, 244.8 ± 26.2 nM, and 202.9 ± 27.2 nM, respectively. The rate of decline of calcium concentration appeared greater as the ACh concentration was increased. The tension induced by ACh was maintained at a constant level for as long as ACh was present even though free calcium declined by _40% from the peak level attained. The tension induced by ACh (10^{-6} M, 10^{-5} M and 10^{-4} M, respectively) was 56.9 ± 4.5%, 87 ± 5.2%, and 100% of maximum. We conclude that the magnitude of the tension induced by ACh is better correlated with the peak calcium concentration attained than the plateau level. (Sppt: by MS Lung Assoc. and NIDA 05094).

43.16

SYMPATHETIC STIMULATION OR ADRENERGIC AGONISTS DO NOT AFFECT TRANSMISSION THROUGH TRACHEAL PARASYMPATHETIC GANGLIA IN CATS. Robert A. Mitchell, Dorothy A. Herbert*, and David Jordan*. University of California, San Francisco, CA 94143-0542

It has been suggested that the sympathetic innervation and/or circulating catecholamines may modulate transmission through tracheal parasympathetic ganglia (TPG). We previously demonstrated in cats that TPG cells innervating smooth muscle fire with inspiratory modulation, paralleling phrenic activity (PA). In anesthetized, paralyzed, artificially ventilated cats, we determined the effect of sympathetic stimulation (SS), isoproterenol (ISO) and norepinephrine (NE) on transpulmonary pressure, PA, membrane potential (MP) and input resistance (IR) of TPG cells. Bilateral SS(N=11) at strengths sufficient to abolish vagal smooth muscle tone, 5ug NE I.V. (N=8), or 5ug/kg ISO I.V. (N=7) had no effect on MP, IR, the afterhyperpolarization, or frequency of EPSPs. In 2 cells SS and ISO both caused a delayed increase in firing and PA at maximal smooth muscle relaxation and in 2 cells NE evoked a delayed decrease in firing and PA at the peak of blood pressure increase. All other cells had no change in firing. We conclude that in the cat SS, ISO, and NE have no direct effect on ganglionic transmission.

43.17

MODULATION OF VASOACTIVE INTESTINAL PEPTIDE (VIP) AND NEURALLY MEDIATED NONADRENERGIC NONCHOLINERGIC (NANC) INHIBITORY RESPONSES BY PEPTIDASE INHIBITION IN GUINEA PIG TRACHEA.

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VIP has been proposed as a mediator of airway NANC inhibitory responses. The present study considers the role of enzymatic degradation in the regulation of these inhibitory stimuli by assessing the susceptibility of responses induced by VIP or NANC inhibitory nerve stimulation to peptidase inhibitor treatment. Ring segments of guinea pig trachea were mounted in organ baths containing modified Krebs solution maintained at 37°C and gassed with 5% CO_2 in O_2. Isometric responses were obtained in tissues treated with atropine, guanethidine, propranolol and indomethacin and in which tone had been induced with histamine. VIP-induced relaxation responses were unaffected by aprotinin, leupeptin, thiorphan and enhanced by soybean trypsin inhibitor. NANC inhibitory responses were unaffected by aprotinin or soybean trypsin inhibitor and attenuated by thiorphan and leupeptin. In tissues depleted of endogenous tachykinins, thiorphan failed to affect NANC inhibitory responses. These data suggest (i) VIP is subject to metabolism by a soybean trypsin inhibitor-sensitive peptidase and (ii) the NANC inhibitory neurotransmitter is not degraded by peptidases susceptible to the inhibitors used in the present study. *DCT is a Parker B. Francis Fellow in Pulmonary Research. This work was supported by PHS Grant HL27025.*

43.18

CHARACTERIZATION OF NEURONS IN THE MUSCULAR PLEXUS OF FERRET TRACHEAL GANGLIA. R.D. Dey* and R.F. Coburn. Dept. of Anatomy, West Virginia Univ., Morgantown, WV, 26506 and Dept. of Physiology, Univ. of Pennsylvania, Philadelphia, PA, 19104.

Innervation to tracheal smooth muscle originates in part from intrinsic neurons present either in large (20 to 60 neurons) ganglia associated with interganglionic nerve trunks (IGNT) or in small (2 to 6 neurons) ganglia present in the muscular plexus on the posterior surface of the trachealis muscle. We have examined neuropeptide content, morphology and electrophysiology of neurons in ganglia of the muscular plexus. Immunocytochemical studies revealed that some of these neurons contained VIP and SP. Frequently, both peptides were present in the same neuron. Five cells, identified by injecting lucifer yellow, were studied electrophysiologically. Resting membrane potentials were between -25 and -60 mV and input resistances varied between 10 and 15 Mohm. Although no fast postsynaptic potentials were demonstrated, 1 to 2 Hz stimulation of IGNT resulted in slow depolarization of the membrane which summated. Morphologically, the neurons were unipolar, branching into multiple transversely oriented axons associated both with smooth muscle and with other ganglia. Thus, the neurons in ganglia of the muscular plexus may provide peptidergic neuroregulation of tracheal smooth muscle activity by direct inputs or by interaction with neurons of other ganglia. Supported by NIH-NHLBI #HL35812 and #HL37498.

CARDIAC DYNAMICS AND ELECTROPHYSIOLOGY

44.1

RIGHT ATRIAL CONTRACTION INCREASES IN PATIENTS WITH MYOCARDIAL INFARCTION

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In the infarcted heart involving the LV inferior wall and/or the ventricular septum, RV rapid filling is impaired. The question is how the RA compensates for impaired RV filling in this interest. We validated the biplane cinegraphic measurement of RA volume from 16 cadaver casts. The calculated volumes by Simpson's rule method agreed well with the true volumes(r=0.99). In age-matched patients with normal sinus rhythm, 19 with normal heart(N-group) and 19 with old myocardial infarction (MI-group), we filmed the RA by biplane cineatriography to construct a time-volume curve every 20 msec. The RA active contraction volumes were significantly larger in MI-group than in N-group(18.6+2.3(mean+SD)ml/m^2 vs 14.5+2.5, p<0.01). The RA active contraction volume(y) increased as a function of RA volume at the beginning of RA active contraction (x) which is the "preload" of the RA (y=0.25x+10.1, r=0.70). We conclude that RA active contraction volume increases in patients with myocardial infarction by augmenting the "preload" of the RA(Frank-Starling mechanism).

44.2

CHARACTERIZATION OF RIGHT VENTRICULAR PRESSURE PARAMETERS USING A FULLY IMPLANTABLE DYNAMIC PRESSURE TRANSDUCER IN DOGS. Mark K. Erickson*, Tom D. Bennett. Pacing Research, Medtronic, Inc., Minneapolis, MN 55430.

The right ventricle (RV) can safely retain chronically implanted, lead-based devices for many years. We studied the chronic behavior of RV pulse pressure (PP) and RV dP/dt max (dP/dt) using a new implantable dynamic pressure transducer (DPT) which connects to an associated telemetry module/pacemaker. The module paced the heart-blocked dogs chronically at 100 bpm and energized the DPT for 200 msec every cardiac cycle. Exercise responses of telemetered DPT signals were evaluated at 1,3, and 6 months after implant in six mongrel dogs. Exercise responses (EX) at 4 mph, 6% grade were:

Rest	1 mo	3 mo	6 mo	EX	1 mo	3 mo	6 mo
PP(mmHg)	48.2±5.0	50.8±2.7	44.9±11.9		60.9±3.7	61.2±4.3	54.0±15.6
dP/dt (mmHg/s)	732±122	755±70	602±110		1026±125	1019±92	892±154

Data are means ± standard deviations. There was no significant differences in PP or dP/dt over time (P>0.05) Chronic DPT signals were also compared directly to simultaneous recordings from Millar Microtip pressure transducers under Halothane anesthesia before and during administration of dobutamine (4.4 ± 0.9 ug/min/kg):

	1 Month		3 Month		6 Month	
	Control	Drug	Control	Drug	Control	Drug
DPT PP	26.7±6.4	40.3±14.2	24.3±2.8	37.0±8.5	20.1±3.6	31.2±9.8
Millar PP	29.2±8.2	38.0±11.0	27.0±4.5	35.5±7.3	21.6±4.8	29.7±7.7
DPT dP/dt	421±112	748±846	334±42*	581±178	257±65	433±131
Millar dP/dt	451±115	846±377	389±49*	699±249	302±54	445±104

*P<0.05 for DPT vs Millar. Thus, RV PP and dP/dt change over a wide physiologic range during exercise testing and during inotropic drug administration and DPT provides reliable chronic (6 month) measurement of these parameters.

44.3

A GENETIC DECREASE OF CARDIAC STROKE VOLUME IN MALIGNANT HYPERTHERMIA SUSCEPTIBLE PIGS.

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All animals were anesthetized with 22 mg/Kg Pentothal with 60% N_2O:O_2 for cutdowns and invasive monitoring with Opticath and Millar catheters recorded on a Hewlett Packard 8-channel recorder. Cardiac output was measured by thermodilution. Body weights of MHS pigs (N=7) were 126.58 Kg with Control #1 pigs (N=6) at 58.03 Kg and Control #2 pigs (N=6) at 120.45 Kg. Statistical tests were run on SPSSPC+. Inbred MHS pigs had a markedly reduced (63.5%) stroke volume index (0.7 ml/beat/Kg) ($P<0.05$) when compared to two groups of control pigs (1.1 ml/beat/Kg). The cardiac index of MHS pigs at 86.23 ml/min/Kg ($P<0.05$) was 66% of the 130.25 ml/min/Kg value recorded in control pigs. The stroke volume of MHS pigs was 38.85 ml/beat ($P<0.05$) as compared to 60.76 ml/beat in control pigs. This data provides a pathophysiologic basis for the well known stress susceptibility of MHS pigs. The inbred MHS pig expresses the pathophysiologic effect of the MH gene(s) defect more acutely than what has ben observed in human MH cases and is a superb animal model for MH. Decreased cardiac pumping capability (63.5% of normal), increased heart rates (up tp 225 bpm), and an intense peripheral vasoconstriction that shuts down heat loss via skin coupled with high metabolic rates(10 to 15x normal) and high core temperatures (up to 48.2°C) are all part of the acute Malignant Hyperthermia Syndrome. Our data suggests that the MH gene defect affects several physiologic systems and is not limited to skeletal muscle.

44.4

TECHNIQUE OF ISOLATION EFFECTS THE CONTRACTILE FUNCTION OF RABBIT HEARTS.

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The inability to consistently preserve adequate cardiac function over a prolonged period contributes to the shortage of donor organs, limiting heart transplantation. The ability to preserve myocardial function may, however, be determined, in part, by the method used to isolate the heart. These experiments examine the effect of the isolation technique on the contractility of hearts. The first set of hearts (n=15) was isolated from New Zealand white rabbits following the administration of a lethal dose of sodium pentobarbitol. The hearts were rinsed with warm (26°C) cardioplegia and, at 80 mmmHg, infused with 50 ml warm cardioplegia, followed by 50 ml cold (5°C) cardioplegia. The second group (n=11) was anesthesized with sodium pentobarbitol and placed on a respirator. The hearts were isolated following in situ administration of cold cardioplegia via the abdominal aorta at 80 mmHg for two minutes. Contractility of the first group of hearts (systolic pressure at 10 mmHg diastolic pressure, measured via standard Langendorff techniques) was 122±5.3; that of the second was 140.64±2.1. The significant difference between these two groups ($p<0.005$) demonstrates that the technique used to isolated hearts effects the contractility of the heart. These data suggest that the technique used to isolate a heart may be a significant determinant of the success of the method used to preserve that heart.

44.5

THE EFFECT OF AGE ON LEFT VENTRICULAR COMPLIANCE IN FISCHER 344 MALE RATS.

Brenda J. Rongish* and Robert J. Tomanek. Univ. of Iowa, Iowa City, IA 52242

Compliance (change in volume that accompanies a change in pressure, or the reciprocal of stiffness) affects several aspects of cardiac function, e.g. contractility, coronary blood flow, and ventricular filling. To test the hypothesis that compliance is altered during aging, we determined pressure-volume relationships in isolated perfused hearts from 14 month (middle-aged) and 24 month (senescent) Fischer 344 male rats. Hearts were placed on a Langendorff apparatus and left ventricular compliance was measured in non-beating hearts perfused with Krebs-Henseleit buffer. A latex balloon inserted into the left ventricle was infused with saline to obtain pressure-volume curves. The two age groups had comparable left ventricular weights (14 mo=0.96 g; 24 mo=0.96 g). The following data represent mean pressures for a given volume ± standard errors:

Volume (μl)		80	90	100	110
14 mo	(n=8)	33±4	38±5	43±5	48±4
24 mo	(n=7)	42±4	49±5	55±6	54±4
P		0.07	0.06	0.07	0.15

Although the results indicate that left ventricular compliance is not markedly altered in senescence, there is a trend for decreased compliance in the old (24 mo) age group compared to the middle-aged (14 mo) group. (Supported by NIH grant HL 18629.)

44.6

LOW OXYGEN AFFINITY BLOOD ATTENUATES CARDIAC MECHANICAL DYSFUNCTION DURING FLOW RESTRICTED OXYGEN DELIVERY.

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The effects of blood oxygen affinity (BOA) on heart function during controlled oxygen delivery (O2D) was studied in anesthetized pigs (n=6). BOA was altered by hemoglobin carbamylation (high BOA) and osmotic-pulse induced inositol hexaphosphate incorporation (low BOA). Coronary blood flow (CBF) was controlled in a by-pass circuit between carotid and left anterior descending coronary arteries. At baseline CBF was 1.26±0.10 ml/min/g (O_2D = 16.3±2.6 ml O_2/min/100 g), regional myocardial fractional shortening (FS) was 15.3±1.0%, and global left ventricle contractility (dP/dt) was 1633±174 dyne x s/cm^5. 50% reduction in O_2D decreased FS by 83.5±11.8% in 2 high BOA pigs (P_{50} = 23.5±0.3) while in 2 low BOA pigs (P_{50} = 33.8±0.4) FS declined by 69.0±13.6%. As CBF decreased 25% more, below 0.5 ml/min/g, dP/dt fell by 23±16% in high BOA pigs but remained unchanged in low BOA pigs. Increased BOA was also associated with higher heart rate (176±3 beats/min) when compared to low BOA animals (145±8 beats/min).

These preliminary results indicate that cardiac function during reduced oxygen delivery can be altered by changing the oxygen affinity of blood.

44.7

CARDIAC CRYOLESION AS AN EXPERIMENTAL MODEL OF VENTRICULAR HYPOKINESIA.

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The lack of a long-term model to simulate clinical ventricular dysfunction has stimulated the study of ischemic and cold injuries to the myocardium. Dogs purchased from a licensed vendor under humane care and proper anesthesia were prepared for sterile surgical procedures. Hearts were exposed after sternotomy and subjected to ischemic or freeze-thaw injuries. A permanent ischemic injury was generated by two-stage ligation of the left anterior descending coronary artery and its first diagonal branch. After 30 minutes, 0.5 ml of sterile mineral oil was slowly injected into the distal side of the ligatures to prevent collateral and retrograde flow. A permanent transmural cryoinjury was produced by a 5 cm diameter cryoprobe cooled to -160°C with internally circulating liquid nitrogen. Both methods resulted in an area of cyanotic, edematous and diskinetic myocardium. The extent of infarction produced by ischemia depends on the coronary arterial anatomy supplying the region, and the early attrition (~40%) due to tachyarrhythmias make ischemia a less desirable model. Cryoinjury produced damaged myocardium of controllable size, depth, and location. A sharp demarcation between injured and uninjured tissue can be clearly observed. Arrhythmia related death was not observed after cryoinjury, and the damaged myocardium healed into a non-contractile scar with little disruption of surrounding myocardium. We concluded that cryolesion can be an experimental model for ventricular hypokinesia.

44.8

RIGHT VENTRICULAR FREE WALL REGIONAL TENSION AND FUNCTION DERIVED FROM MAGNETIC RESONANCE IMAGES.

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Right ventricular free wall (RVFW) tension has not been measured, due to its irregular geometric shape and the complex material properties of the myocardium. Since the RVFW thickness is small, the mechanics of thin shells can be used to calculate the wall tensions. This method only requires knowledge of surface curvature to calculate the direction and magnitude of the wall tensions. Using ECG gated magnetic resonance imaging (MRI) we reconstructed the endo- and epicardial surfaces of the entire heart non-invasively using 3D computer graphics. Because of its irregular shape, curvature of the RVFW is calculated locally using bi-quadric surface patches. From the 3D computer images the RVFW was graphically isolated and local curvatures and tensions calculated for the entire RVFW surface. The directions and magnitudes of the tensions were represented as vectors superimposed on 3D images of the RVFW, similar to the vector plots used in engineering to visualize fluid flow. Local wall thicknesses were also calculated and used along with local tensions to evaluate regional wall function. This method can be used to analyze the function of the normal and diseased heart, including right myocardial infarction and positive end-expiratory pressure. 3D images of the RVFW wall tension properties can be used clinically for patient evaluation. This work was supported in part by the American Heart Assoc., Texas Affiliate.

44.9

DESCRIPTION OF RIGHT VENTRICULAR KINEMATICS USING A THREE-DIMENSIONAL COORDINATE SYSTEM. G.H Templeton, M.S. Sacks*, F. Schweip*, and C.J. Chuong*. Univ. of Tex Southwestern Med. Ctr., Dallas. Tx. 75235

The complexity of right ventricular geometry has prevented a simple description of right ventricular contraction. Accordingly, eight mongrel dogs were implanted with eighteen right ventricular markers at three latitudinal levels; twelve were in the free wall and six in the septum. After recovering from sterile surgery for 4-6 wks, marker displacements were imaged by biplane cinefluorography and referenced to different ventricular coordinate systems. 3-D computer graphics were developed to display the markers and their displacements elicited by contraction. Referenced to a ventricular long axis, a linear regression related the systolic latitudes of the markers to their diastolic latitudes; correlation coefficients were greater than 0.96. Consequently, the linear relationship between diastolic and systolic locations of right ventricular landmarks can be applied to imaging by systems such as MRI or echocardiography, which image short-axial or equatorial planes. By using the linear relationship, the latitudinal position of a ventricular landmark during systole can be found knowing its end-diastolic latitude.

44.10

An MRI Based Assessment of Regional Cardiac Mechanics

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In anesthetized dogs and awake normal humans, the total heart volume (THV=total contents of pericardial sac) remains essentially constant throughout the cardiac cycle. To understand regional mechanics serving to maintain a constant THV we are utilizing a non-invasive magnetic resonance imaging based myocardial tagging technique or spatial modulation of magnetization (SPAMM). In 4 normal volunteers we have shown a fixed epicardial apex and a non-isotropic long axis shortening with greatest LV free wall (LVFW) shortening near the base and greatest septal wall shortening midway between base and apex. The angle between mitral and tricuspid annulus changes from 150° to 159° between end-diastole and late systole. The mitral valve moves towards the apex without changing angulation. Pericardial sac (PS) and myocardial labeling demonstrates slippage of the RVFW by 2.5cm in the PS towards the apex in systole. From short axis images, at 25% LV apex-to-base distance, motion is counter clockwise (CC) totaling 18-20°. At a location 75% of the apex-to-base distance, early systolic CC motion reverses in later systole. This motion reversal at the basal region yields a net "wringing", presumably pulling the valve plane apically. In early systole, basal posterior interventicular sulcus segments move clockwise, expand, and may contribute to isovolume.

44.11

A CRITICAL EARLY POSTNATAL PERIOD FOR STRESS-INDUCED ALTERATION OF HEART DEVELOPMENT. David G. Penney and C. Clough Helfman.* Wayne State Univ., Detroit, MI 48201.

Exposure of newborn rats to carbon monoxide (CO) for 30-32 days, results in adulthood in persistent cardiomegaly (PC), persistent tachycardia, increased myocyte numbers and length, and decreased myocyte volume. Could PC be a function of stress-stimulated myocyte hyperplasia? Rat litters were randomly assigned to one of 5 groups: 1) CO from 1-10 days of age, 2) CO from 1-20 days of age, 3) CO from 1-32 days of age, 4) CO from 16-32 days of age, and 5) room air controls (AIR). Right ventricle (RV) mass was increased 65.6%, 63.0%, and 56.6% after 10, 20 and 32 days of 500 ppm CO exposure, respectively, relative to AIR controls. In the 16-32 day group, RV mass was increased only 34.5%. In rats reaching 154-160 days of age, RV mass of the 1-10 day, 1-20 day, and 1-32 day groups were increased 7.3%, 13.0% and 12.2%, respectively, relative to the AIR controls, all signif. increases. RV mass of the 16-32 day group was increased only 2.1% above the AIR controls. Total ventricular DNA content, a marker for myocyte numbers in this model, was signif. increased in the 1-10 day, 1-20 day, and 1-32 day groups relative to AIR group (greatest increase in 1-20 & 1-32 day groups), but was not signif. altered in the 16-32 day group. The data suggest a critical period for PC and cellular remodeling extending from birth till 16-20 days after birth. Our results support the hypothesis of an association between stress-stimulated myocyte hyperplasia and PC.

44.12

CARDIAC EFFECTS OF KT-362, A NEW PUTATIVE INTRACELLULAR CALCIUM ANTAGONIST. Nedilika Buljubasic*, Jure Marijic*, Hanna Eskinder*, John P. Kampine, Garrett J. Gross* and Zeljko J. Bosnjak. Med. Col. of Wisconsin, Milwaukee, WI 53226

The purpose of this study was to determine direct cardiac effects of KT-362 (5-[3[[-2-C3,H-dimethoxyphenyl)-ethyl]amino]-1-oxoopropyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine fumarate) ($5x10^{-7}$ to $5x10^{-5}$ M), a drug which inhibits the intracellular calcium mobilization. We used spontaneously beating isolated and isometrically contracting guinea pig hearts (n=9). Heart rate, AV time, coronary flow, oxygen consumption, left ventricular pressure (LVP) and its first derivative were measured during spontaneous beating and during cardiac pacing at 2-7 Hz. KT ($5x10^{-7}$M) did not cause any significant effect on the heart, while 10^{-6}M decreased peak systolic left ventricular pressure (SLVP) and decreased dP/dt. Higher concentrations caused dose-dependent decrease in heart rate, peak SLVP, positive and negative LV dP/dt, oxygen consumption and also caused an increase in AV conduction time. The increase in AV conduction time was exacerbated when hearts were paced, compared with spontaneous rhythm when a pronounced decrease in heart rate antagonized some of the increase in AV time. Only the highest concentration caused an increase in coronary flow and diastolic pressure. All KT effects were completely reversible. (Supported in part by NIH Grant HL01901 and Kotobuki Pharmaceutical Co., Ltd.)

44.13

INTERACTION BETWEEN Ca AND cAMP ON THE INTRACELLULAR LONGITUDINAL RESISTANCE OF RAT CAPILLARY MUSCLE. R. Ping Xiao* and W.C De Mello. Departments of Anesthesiology and Pharmacology, Medical Sciences Campus, San Juan, PR 00936.

Evidence is available that high $[Ca]_i$ decreases junctional conductance in heart (De Mello, 1982). In the present study we investigated the interaction between Ca and cAMP on the intracellular longitudinal resistance (ri) of rat papillary muscle using the action potential method of Weidmann (1970). The results indicated that isoproterenol (10-5 M) added to bath solution decreased ri by 25.5 + 11.7% (n = 10) in a reversible fashion. The blockade of beta-adrenergic receptors with propranolol (10-5 M) increased ri by 48.4 ± 29% (n = 10) and suppressed the effect of isoproterenol on ri. Forskolyn (10-6 M) also reduced ri. When the muscle was exposed to high Ca solutions (6 mM) ri was increased by 72.2 + 38.6% (n = 9). Isoproterenol (10-5 M) plus high Ca solution increased ri instead of decreasing it. The effect of high Ca solution in ri was reduced or reversed by verapamil (10-6 M). These findings not only support the view that cAMP is a modulator of ri but indicate that a balance between Ca and cAMP is involved in the regulation of ri. Supported by Grant No. HL-34148 from NIH.

44.14

ON THE MECHANISM OF THE DIFFERENT SENSITIVITY OF PURKINJE AND MYOCARDIAL FIBERS TO STROPHANTHIDIN. G. Iacono* and M. Vassalle. SUNY, Health Sci. Ctr., Brooklyn, N.Y. 11203.

The mechanism of the different sensitivity of Purkinje and myocardial fibers to strophanthidin ("stroph") was studied in vitro. Membrane potentials, force and, in some experiments, intracellular sodium activity (a^i_{Na}) were recorded under different sodium loads in the absence and presence of stroph. Stroph (0.2 μM) increased force percentagewise more and at a faster rate in Purkinje than in myocardial fibers. Tetrodotoxin (TTX, 2 μM) markedly reduced whereas high $[Na]_o$ (176.6 mM) and veratridine (0.2 μM) potentiated stroph inotropy in Purkinje but not in myocardial fibers. The rate of force development was augmented by high $[Na]_o$ and veratridine in Purkinje fibers but little (veratridine) or not at all (high $[Na]_o$) in myocardial fibers. Stroph lengthened the plateau in Purkinje and shortened it in myocardial fibers. TTX, high $[Na]_o$ and veratridine affected the action potential duration more in Purkinje than in myocardial fibers. TTX decreased far more and stroph reincreased a^i_{Na} less in Purkinje fibers. Stroph increased a^i_{Na} similarly in high $[Na]_o$ and veratridine in the two tissues. Thus, in Purkinje fibers action potential and force are more sensitive to changes in Na influx and the greater sensitivity to stroph appears to be due to a greater Ca influx related to the longer plateau and not to a greater increase in a^i_{Na}. Supported by N.I.H. grant HL 17451.

44.15

STRONTIUM INDUCES OSCILLATORY POTENTIALS IN SHEEP CARDIAC PURKINJE FIBERS Mario D. Gonzalez* and Mario Vassalle. SUNY, Health Science Center, Brooklyn, N.Y. 11203.

The mechanism by which calcium overload induces an oscillatory potential, a prolonged depolarization and repetitive activity was studied by exposing Purkinje fibers perfused in vitro to different concentrations of strontium. The results show that strontium: 1) can induce an oscillatory potential (V_{os}) and repetitive activity at low concentrations (1.35-2.7 mM); 2) at high concentrations (5.4-10.8 mM) causes less frequently a distinct V_{os} but during recovery in Tyrode solution a large V_{os} appears as Sr overload recedes; 3) decreases the maximum diastolic potential by inducing a prolonged depolarization (V_{ex}) that subsides slowly during a temporary interruption of the drive; 4) induces a larger V_{ex} after procedures that increase Sr loading (fast driving rates, higher Sr concentrations or longer action potentials); 5) does not induce V_{os} and V_{ex} in the presence of slow channel blockers; 6) exchanges with Na since in low Na solution the twitch amplitude increases in spite of a shortening of the action potential; 7) needs Na as charge carrier since the slope of diastolic depolarization decreases in low $[Na]_o$. It is concluded that, in the absence of Ca, Sr induces an oscillatory potential and the prolonged depolarization V_{ex} by inducing Sr overload and that an electrogenic extrusion of Sr in exchange for Na is the mechanism underlying both V_{os} and V_{ex}. Supported by N.I.H grant HL 27038.

44.16

ON THE MECHANISM OF INCREASED POTASSIUM CONDUCTANCE BY THE POTASSIUM CHANNEL OPENER BRL 34915 IN ISOLATED VENTRICULAR MYOCYTES. B. Liu*, J.R. McCullough* and M. Vassalle. SUNY, Health Science Center, Brooklyn, N.Y., 11201 and Squibb Institute for Medical Research, Princeton, N.J. 08543.

The potassium channel involved in the effects of BRL 34915 was studied in single guinea pig ventricular myocytes using a whole cell voltage clamp technique. In control, the late current-voltage relation showed a distinct inward rectification. BRL (1-100 μM) shortened the action potential and diminished or abolished inward rectification but had no effect on currents flowing during hyperpolarizing clamp steps. BRL did not decrease I_{si} but accelerated the time constant of activation and amplitude of the outward current. Cd (2 mM) markedly decreased I_{si} and BRL induced a rapid outward shift of late current to a greater value. Glybenclamide (10 μM), a blocker of ATP-sensitive K^+ channels, had little effects of on action potential, membrane currents and I-V relation. However, glybenclamide completely abolished the effects of BRL on action potential and currents, and restored inward rectification. Thus, the mechanism by which BRL shortens the action potential is a quick growth of an outward current due to reduction or abolition of inward rectification of an ATP-dependent K channel. The reduction in force in non-isolated tissues appears due to the shortening of the action potential and not to a decreased I_{si}. Supported by N.I.H. grant Hl 27038.

44.17

DIPYRIDAMOLE'S NEGATIVE CHRONO- AND DROMOTROPIC EFFECTS IN ISOLATED PERFUSED GUINEA PIG HEARTS ARE ASSOCIATED WITH INCREASES IN ADENOSINE AND DECREASES IN INOSINE RELEASE. Lois Jane Heller, Richard A. Nelson*. University of Minnesota, Duluth, MN 55812

Dipyridamole is thought to potentiate the various actions of endogenous adenosine by blocking its uptake into cardiac cells and thus increasing interstitial [ADO]. If deamination to inosine (INO) is an intracellular event, it follows that dipyridamole should also decrease interstitial [INO]. To assess this possibility, we monitored the [ADO] and [INO] in the venous effluent of isolated guinea pig hearts perfused at constant flow. The addition of 10 μM dipyridamole to the perfusate significantly increased [ADO] (46±15 to 147±48 nM), and decreased [INO] (326 ± 55 to 228 ± 27 nM). These changes were associated with decreased atrial rate (to 88±4 % of control), increased PR interval (to 120±4 % of control) and AV nodal blocks in 2 of 7 hearts. The presence of the extracellular adenosine receptor antagonist, 8-(4-sulfophenyl)theophylline (10 μM), eliminated the dipyridamole-induced decrease in atrial rate and incidence of AV block and attenuated the increase in PR interval (to 108±3% of control) but did not affect the dipyridamole-induced alterations [ADO] and [INO]. These data support the suggestions that 1) dipyridamole blocks ADO uptake and subsequent intracellular deamination to INO and 2) the negative chronotropic and dromotropic effects of dipyridamole are a result of increased extracellular [ADO].

Supported by NIH grant HL 34351.

44.18

CURARE CAUSES DIRECT CARDIAC RELEASE OF HISTAMINE AND ADENOSINE. D.F. Stowe, J. F. Gualtieri*, D.L. Roerig, and J.P. Kampine. Departments of Anesthesiology and Physiology, The Medical College of Wisconsin, Milwaukee, WI 53226

Tubocurarine (TC) is known to cause tissue release of histamine (HN) *in vivo*. In the heart HN produces positive chronotropic and inotropic effects, prolongs AV conduction and can lead to AV block. Adenosine (ADE) also slows AV conduction. We determined if TC stimulates ADE as well as HN release. Four guinea pig hearts were isolated and perfused with oxygenated Krebs-Ringer solution. Heart rate (HR), AV time, left ventricular pressure (LVP) and coronary flow (CF) were measured before and after bolus injection of 1 mg TC. Coronary effluent was sampled at 30 s intervals for HN, ADE and inosine (INO) using extraction and HPLC methods. TC immediately (5 s) increased LVP (control 98 torr) by 28% and AV time (control 58 ms) by 32%; at 30 s HR fell 15%; AV block occurred (100%); LVP decreased 50% and CF increased 50%; within 6 min all values returned to control except AV time. Baseline HN (90 pg/ml) increased 5.8 times at 30 s; 2.8 times at 3 min and remained at 1.4 times control at 6 min while baseline ADE (4 ng/ml) increased 1.3 times at 30 sec; 3.8 times at 3 min and remained at 2.3 times control at 6 min. Baseline INO (14 ng/ml) increased proportionally to ADE. These studies show that TC causes direct cardiac release of HN and suggests that the delay in AV conduction attributed to HN is due, at least in part, to concomitant release of ADE. (AHA, WI Affl.)

ENDOTHELIUM-DEPENDENT RESPONSES

45.1

NITRIC OXIDE CAUSES HYPERPOLARIZATION AND RELAXATION OF ARTERIAL SMOOTH MUSCLE. M. Tare*, H.C. Parkington*, H.A. Coleman*, T.O. Neild* and G.J. Dusting* (SPON: J.H. Szurszewski). Monash Univ., Clayton, Vic., Australia 3168

Acetylcholine (ACh) stimulates the vascular endothelium to release a humoral factor that causes vasorelaxation which, in many arteries, is accompanied by hyperpolarization. Endothelium derived relaxing factor (EDRF) is closely related to nitric oxide and is responsible for the relaxation. We investigated whether EDRF also caused hyperpolarization in uterine arteries from guinea pigs. Membrane potential and isometric tension were measured simultaneously in ring segments of artery mounted on a Mulvany-Halpern style myograph. The arteries were depolarized and constricted with 0.05-10μM phenylephrine. ACh (1-10μM) evoked hyperpolarization and relaxation, both of which were abolished by removal of the endothelium. NO (0.1-20μM) caused hyperpolarization and relaxation that mimicked those evoked by ACh. The nitrovasodilators, sodium nitroprusside (10μM) and nitroglycerine (10μM) also hyperpolarized and relaxed these arteries. N-monomethyl-L-arginine (NMMA) is an inhibitor of EDRF biosynthesis. NMMA (1-20μM) reduced both hyperpolarization and relaxation in response to ACh. These actions of NMMA were abolished by preincubation of the arteries with 100μM L-arginine, the proposed precursor of NO. A single factor, EDRF, which is closely related to NO is released from the endothelium and mediates both hyperpolarization and relaxation in these arteries.

45.2

CELLULAR MECHANISMS UNDERLYING CHOLINERGIC VASODILATATION. Stephen T. O'Rourke* (Spon: Galen M. Pieper). Medical College of Wisconsin, Milwaukee, WI 53226.

Acetylcholine (ACh) causes relaxation of blood vessels by stimulating the release of relaxing factor(s) from the endothelium or by inhibiting the release of norepinephrine from adrenergic nerves. This study was designed to compare the receptor mechanisms underlying these responses to ACh. Rings of canine saphenous vein (SV) and left circumflex coronary artery (LCX) were suspended for isometric tension recording in organ chambers. The tissues were contracted either with 2Hz electrical stimulation (SV; endothelium removed) or with $PGF_{2\alpha}$, $2x10^{-6}M$ (LCX, endothelium intact). ACh produced relaxations which were inhibited in a competitive manner by pirenzepine, AF-DX 116 and 4-DAMP in both preparations. Schild analysis of these data provided the following pA2 values (SV and LCX, respectively): pirenzepine=6.5 and 6.8; AF-DX 116=7.2 and 6.2; and 4-DAMP=8.0 and 9.0. Pretreatment of the tissues with the protein kinase C activator, phorbol 12-myristate 13-acetate ($10^{-8}M$), inhibited the response to ACh in the LCX, but not in the SV. These data suggest that endothelium-dependent relaxation in the LCX is mediated by M_3-receptors which may be regulated by protein kinase C. In the SV, M_2-receptors mediate the inhibition of norepinephrine release from adrenergic nerves; these receptors do not appear to be regulated by protein kinase C.

45.3

N-METHYLARGININE AUGMENTS ACTIVE ISOMETRIC CONTRACTION OF RAT AORTA IN VITRO. JG Umans* and AP Metkus* (Spon: MD Lindheimer). Section of Nephrology, University of Chicago, Chicago, IL 60637.

N-methylarginine (NMA) blocks endothelium (E) dependent relaxation in guinea pig and rabbit vessels and raises arterial pressure by inhibition of EDRF biosynthesis. We used NMA as a probe of basal and agonist-induced EDRF release from rat thoracic aortic rings, in vitro. All rings were studied at their optimum resting tension in oxygenated Krebs buffer with 10 uM indomethacin. NMA (0.25 mM) blocked E-dependent relaxation due to 10 uM ACh and induced both leftward shifts in dose-effect curves and increased maximal contractions for phenylephrine (PE) > KCl or endothelin. NMA had no significant vasoconstrictor effect in the absence of active tone. The increase in contraction elicited by NMA was E-dependent, ranged in magnitude from 12 to 154% of a maximal PE-induced contraction, and was inversely proportional to predrug active tension. Methylene Blue (MB, 10uM) induced an increase in contraction significantly ($p<0.05$) greater than that due to NMA. In contrast to the augmentation of contraction due to NMA, the effect of MB was not reversed by L-arginine (2.5 mM) or repeated washing. Furthermore, NMA augmentation of active tension (PE, ED 20 dose) was a more sensitive indicator of endothelial function than is relaxation to 10 uM ACh. Supported by Schweppe Fdn, Chicago Heart Assoc, and PMA Fdn.

45.4

EDRF AND BRADYKININ-INDUCED DILATION OF SMALL INTESTINAL MICROVESSELS IN THE RAT. L.S. UNGER*, N.L. ALSIP, AND P.D. HARRIS. Ctr. Appl. Microcir. Res., Univ. of Louisville, Louisville KY 40292.

Acetylcholine (ACH)-induced dilation of small intestinal (SI) 3rd-order arterioles appears to be EDRF independent (Unger et al., 1989). This study measures SI large (A1) and small arteriolar (A3) responses to bradykinin (BK) before and after hydroquinone (HQ) to inactivate EDRF in anesthetized rats (n=5). A loop of small intestine with intact nerve and blood supplies was suspended over an optical port in an environmentally controlled tissue bath. Arterioles were observed by in vivo videomicroscopy during sequential administration of BK (10-8 to 10-5M) to the bath in the presence (HQ-BK) and absence (BK) of HQ (5X10-4M). Nitroprusside was added to test the dilator capacity (MAX) of these vessels. Data are reported as % of MAX-minus-baseline (BL), or MAX-minus-HQ (* $p< 0.05$ BK vs HQ-BK).

	BL (um)	10-8M	10-7M (% of MAX)	10-6M	10-5M	MAX (um)
$A1_{BK}$	92±5	24±10	88±7	90±6	92±3	130±4
$A1_{HQ-BK}$	72±5	22±11	43±10*	82±8	92±6	---
$A3_{BK}$	30±3	31±13	51±19	89±5	94±4	50±6
$A3_{HQ-BK}$	27±4	43±8	55±17	91±4	88±7	---

Small A3 dilation by BK was unaffected by HQ. Large A1 dilation by BK was blunted by HQ. Thus, EDRF appears to mediate large but not small arteriolar dilation in the SI.

45.5

EVIDENCE AGAINST ENDOTHELIUM DERIVED RELAXING FACTOR(S) IN TROUT ARTERIES. K.R. Olson. Indiana Univ. School of Medicine, South Bend Center, Univ. of Notre Dame, Notre Dame, IN 46556.

Isolated vascular rings were prepared from the elastic, pregill ventral aorta (VA) or post gill celiacomesenteric artery (CM) of 2-4 Kg steelhead trout (Salmo gairdneri). Rings were equilibrated with 1g (VA) or 0.75g (CM) resting tension in phosphate buffered ringer (pH, 7.8; 14°C) for 1 h. Tension was monitored with a Grass force transducer. Acetylcholine (Ach) produced dose-dependent contractions (DDC) in both vessels, where as epinephrine (E) or norepinephrine (NE) produced DDC only in CM. VA did not respond to E or NE. Unstimulated or partially contracted ($E = 3x10^{-8}M$) CM arteries, with or without endothelium, did not relax in response to Ach (10^{-10} to $10^{-6}M$), bradykinin (Bk; 10^{-10} to $10^{-7}M$), methylene blue (Mb; $10^{-5}M$) or the calcium ionophore, A23187 (10^{-9} to $10^{-6}M$); Ach, Bk and A23187 increased tension at higher concentrations. Unstimulated or Ach contracted VA, with or without endothelium did not relax in response to Bk, Mb or A23187. Sodium nitroprusside (Np; $10^{-6}M$) or atrial natriuretic factor (ANF; rat [Ile^{26}]; $10^{-8}M$) relaxed agonist induced contractions in both VA and CM. These results show that trout arteries exhibit specific sensitivity to classical smooth muscle agonists. The results also suggest that trout arterial endothelium does not release relaxing factors through mechanisms similar to those found in mammals. Supported in part by NSF Grant No. DCB-8616028.

45.6

PLATELET ACTIVATING FACTOR (PAF), NEUTROPHILS AND ENDOTHELIUM-DEPENDENT RELAXATION (EDR). Galen M. Pieper and Garrett J. Gross. Medical College of Wisconsin, Milwaukee, WI 53226.

Endothelial cells can be damaged by activated polymorphonuclear leukocytes (aPMNs). We tested whether PAF, 1-0-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine promoted PMN-induced injury to EDR. Isometrically-suspended rat aortic rings were incubated for 15 or 20 min with unstimulated PMNs (uPMNs) or aPMNs using the chemotactic peptide, FMLP, and cytochalasin B. After washing the incubate, maximum EDR to acetylcholine in $PGF_{2\alpha}$-contracted rings were: 46±6% (uPMN), 52±8% (15 min aPMN) and 22±7% (20 min aPMN). Incubation of aPMNs (15 min) with PAF (10 nM) unmasked injury to EDR (30±5%) to acetylcholine without altering relaxation to nitroglycerin, an endothelium-independent vasodilator. Either catalase (56 U/ml) or the PAF antagonist, CV-3988 (50 μM), used alone blocked the impaired EDR. Thus, PAF primes PMNs to injure EDR by a PAF receptor-stimulated process which involves oxygen-derived free radicals.

45.7

STIMULATION OF CYCLIC GUANOSINE-3',5'-MONOPHOSPHATE (cGMP) PRODUCTION BY METHYLCHOLINE DIFFERS IN AORTAE FROM PREGNANT AND VIRGIN RATS. Susan L. Whittemore* and Kirk P. Conrad. Dartmouth Med. School, Hanover, NH 03756

Aortic production of cGMP has been demonstrated to correlate well with endothelium-dependent relaxation as mediated by endothelium-derived relaxing factor (EDRF). Because rat (and human) pregnancy is characterized by vasodilation, we examined cGMP production of aortae from pregnant and virgin rats. Six aortic rings from each rat were equilibrated in Krebs Buffer with 5mM glucose, 20mM HEPES and 9% dextran and gassed with 5% CO2/ 95% room air for 2 hrs prior to treatment. Incubations were terminated with liquid N2. After tissue extraction, cGMP was determined by RIA. Basal cGMP levels did not differ between pregnant (gestational age: 11 to 21 days) and age-matched virgin animals (689 ± 48 and 774 ± 21 pmol cGMP/mg protein, respectively) and were reduced similarly after a 10 min incubation with 10-5 M hemoglobin (166 ± 18 vs 177 ± 21 pmol cGMP/mg protein). However, cGMP production by aortic rings from gravid rats was greater (P=0.001 by ANOVA) than that of rings from virgin controls upon stimulation with 10-5M methylcholine.

	15 sec	30 sec	60 sec	120 sec
Pregnant *(n=18)*	2575±518*	4093±617**	4199±592*	1987±294
Virgin *(n=18)*	1337±239	2190±404	2432±352	1455±254

*(values are % control,mean and SEM. * P<0.05. ** P<0.01)*

Production of cGMP by aortic rings from pregnant and virgin rats did not differ when stimulated with 10-4 M sodium nitroprusside. Taken together, these data suggest increased potential for EDRF activity during pregnancy. (HL 38076, HD 00662, DK 07301, 8th Mallinckrodt Scholar Award)

45.8

EFFECT OF ENDOTOXIN ON INTRINSIC REACTIVITY OF VASCULAR TISSUE. *ME Wylam, *RW Samsel, *JG Umans, RW Mitchell, AR Leff and PT Schumacker. Dept. of Med., Univ. of Chicago, Chg, IL 60637.

Sepsis is known to cause morphologic injury to endothelial cells. Endothelial cells perform important physiologic functions influencing vascular smooth muscle tone through the action of endothelial-derived vasoactive factors. Previously, we demonstrated an impaired ability of the isolated intestine to extract oxygen from a limited O_2 supply, and a loss of reactive hyperemia, in a canine endotoxemic model of sepsis. Matching blood flow to local oxygen demand is essential for efficient O_2 extraction. Conceivably, an imbalance of endothelial-derived vasodilatory and constrictive substances could contribute to the circulatory derangements and tissue O_2 extraction defects seen in sepsis. Our goal was to determine whether endothelial-dependent responses were altered in canine endotoxemia. E. coli endotoxin (5mg/kg i.v.) was administered to anesthetized dogs. After 4-5 hours isolated rings of femoral, renal and mesenteric artery were mounted for isometric tension recordings. The rings were equilibrated and contracted with phenylephrine at concentrations eliciting a 50% maximal contraction, as determined from cumulative concentration response curves. The acetylcholine concentrations necessary to reduce this tension by 50% were:

	Control (pD_2 values)	Septic	
Femoral	8.091±.188M	7.384±.137M	p<.005
Renal	7.806±.175M	6.966±.269M	p<.05
Mesenteric	7.953±.149M	7.264±.043M	p<.002

Thus, "septic" arteries were less sensitive to acetylcholine mediated endothelial-dependent relaxation. Endothelial independent relaxations elicited by sodium nitroprusside were not different, nor was contraction elicited with K^+-substituted Krebs-Henseleit solution. Maximal contractile response to phenylephrine was augmented in "septic" arteries. Hence, endotoxemia *in vivo* impairs endothelial-mediated relaxation of vascular smooth muscle *in vitro*. (HL01857, HL01642, HL32646, and HL32495).

45.9

IMPAIRED VASORELAXATION PROXIMAL AND DISTAL TO AORTIC COARCTATIONS IN RABBITS. David R. Bell and Paul D. Stein. Henry Ford Heart and Vascular Institute, Detroit, MI. 48202

The hypothesis that alterations of fluid dynamics in the region of a stenosis may affect local vascular reactivity was examined. In 13 stenosed (ST) rabbits, a 1.7mm I.D. x 10mm length gold band was placed around the abdominal aorta to alter local fluid dynamics. Four weeks later, aortic strips were mounted in tissue baths and isometric force responses to acetylcholine (Ach) and nitroprusside (NP) were evaluated. Controls were 12 unoperated rabbits. Maximal relaxation to Ach of strips with endothelium (ENDO) below ST were 54±10%, above ST, 62±9% and CON 91±3% ($p<0.01$ above or below ST vs. CON, mean±SEM). In regions of a stenosis, therefore, ENDO mediated vasorelaxation was impaired. Sensitivity of strips to NP (-log M ED50) with ENDO below ST vs CON was 8.72±0.06 vs 8.66±0.08 (NS) and with no ENDO below ST vs. CON was 8.47±0.1 vs 8.70±0.08 ($p<0.05$). NP response below ST, therefore, was impaired in the absence of ENDO and it was normal with ENDO. Thus, ENDO may compensate for lack of response of agents that normally act directly on smooth muscle in regions of hemodynamically impaired vasorelaxation.

45.10

REDUCTION OF PULMONARY ENDOTHELIUM-DEPENDENT VASORELAXATION IN END-STAGE PULMONARY DISEASES. A.T. Dinh Xuan, T.W. Higenbottam, C. Clelland*, J. Pepke-Zaba*, G. Cremona*, J. Wallwork*. Papworth Hospital, Cambridge CB3 8RE, UK.

We tested in vitro endothelium-derived relaxing factors (EDRF)-mediated relaxation of pulmonary arteries (PA) rings obtained at heart-lung transplantation (HLT) in 12 patients: 4 cystic fibrosis (CF), 4 Eisenmenger's syndrome (ES) and 4 end-stage lung diseases (ESLD). Control PA rings were obtained at lobectomy from 10 patients with lung carcinoma but without secondary pulmonary hypertension. Changes in isometric tension in pairs of rings with (E^+) and without endothelium (E^-) were studied after precontraction with phenylephrine (10^{-6}M). No relaxation occurred in all E^- rings whereas it was markedly reduced ($p<0.001$) in E^+ rings of HLT PA to both acetylcholine (ACh) and adenosine diphosphate (ADP) (10^{-10} to 10^{-5}M) compared to control.

max relation	ACh(%)	ADP(%)
CF	32.6 ± 12.3	58.7 ± 7.7
ES	34 ± 11.7	40 ± 10
ESLD	30 ± 10	0
Control	71.8 ± 5.9	83.7 ± 2

We conclude that EDRF-mediated vasorelaxation, though present is markedly impaired in PA of HLT recipients, possibly through histological and/or functional alterations of pulmonary vascular endothelial cells.

CORONARY AND CEREBRAL CIRCULATIONS

46.1

CHARACTERIZATION OF RAT CEREBRAL MICROVASCULAR ENDOTHELIAL CELLS WITH REGARD TO ADENOSINE METABOLISM AND ELECTROPHYSIOLOGICAL PROPERTIES Ellen L. Gordon*, G. Alexander West*, and H. Richard Winn, University of Washington, Harborview Medical Center, Seattle, WA, 98104.

We have recently reported [Physiologist 31:A191 (1988)] a technique to establish rat cerebral microvascular endothelial cells (RCMEC) in culture. We now have investigated the kinetics of uptake and metabolism of adenosine in RCMEC. Additionally, we describe their initial electrophysiologic characterization. The K_m and V_{max} of adenosine uptake (as well as K_i for dipyridamole and nitrobenzylthioinosine) are reported for RCMEC and compared to C6 glioma cells and isolated rat cerebral microvessels. TLC and HPLC analyses were used to determine the ultimate fate of radiolabeled adenosine and the specific activity of the adenine nucleotide and nucleoside pools, both intracellularly and extracellularly. Whole cell and patch clamp electrophysiological studies were conducted in RCMEC, bovine aortic endothelial cells (BAEC) and rat aortic endothelial cells (RAEC). Single channel experiments showed distinct differences in channel density, conductance and open time among these cell types. In conclusion, the results from metabolic and electrophysiologic studies show there are distinct differences in RCMEC compared to other cell types. These observations contribute to a growing body of data indicating endothelial cell function is site and species specific.
(Supported by AHA #88-WA-111, #881134, and NIH #RO1-NS-21076).

46.2

THE EFFECT OF ACETATE AND ETHANOL ON ADENOSINE EFFLUX IN RAT CEREBRAL MICROVASCULAR ENDOTHELIAL CELLS AND C6 GLIOMA CELLS. John D. Day*, Ellen L. Gordon*, and H. Richard Winn. University of Washington, Harborview Medical Center, Seattle, WA 98104.

There is evidence that extracellular concentrations of adenosine (ADO), a potent vasodilator, may be altered by ethanol (EtOH) ingestion. We have studied the acute response of cultured rat C6 glioma cells and rat cerebral microvascular endothelial cells (RCMEC) to EtOH and acetate (EtOH's main metabolite). Cells were preincubated with [^{3}H]-ADO to label their adenine nucleotides, and then challenged with acetate (50-100 mM) or EtOH (100-200 mM). The time and concentration dependent efflux of radiolabel was monitored. In C6 cells extracellular radioactivity (ECR) increased 185% and 377% after 10 min. with 100 and 200 mM acetate, respectively. In contrast, no significant increase in ECR was observed in parallel experiments with RCMEC. Dipyridamole, an ADO transport blocker, inhibited the accumulation of ECR. Interestingly, EtOH resulted in a reduction in ECR in both cell types. TLC analysis revealed ECR consisted of adenosine (ADO), inosine (INO), and hypoxanthine (HX). Inclusion of the ADO deaminase inhibitor EHNA resulted in the decreased conversion of ADO into INO and HX. This work: (1)supports recent reports that EtOH blocks ADO transport, (2)shows that acetate can act as a metabolic stimulus to increase ADO synthesis and release in C6 glioma cells, but not in RCMEC. (Supported by AHA #88-WA-111, #881134, and NIH #RO1-NS-21076.)

46.3

IN VITRO RESPONSES OF RAT INTRACEREBRAL ARTERIOLES TO ADENOSINE ANALOGS AND THEOPHYLLINE. Al C. Ngai* and H. Richard Winn. Univ. of Washington, Seattle, WA 98104

Adenosine (Ado) is implicated in the metabolic regulation of cerebral blood flow. Brain interstitial Ado concentration has been measured and shown to increase in conditions such as ischemia and hypoxia. Yet, little is known about the reactivity of intracerebral vessels to Ado. This study utilized an in vitro technique to examine the responses of intracerebral arterioles to Ado, its analogs, and its antagonist, theophylline (Theo). Penetrating, intracerebral rat arterioles were cannulated with micropipettes and pressurized to 60 mmHg. Vessel diameter was measured with a video micrometer. The vessels developed spontaneous tone in buffered saline (pH 7.3) at 37°C. Viability was assessed by reactivity to hydrogen ion. Increasing concentrations of Ado, inosine, and Theo were applied extraluminally. These vessels were highly responsive to Ado (threshold=10^{-8}M, EC_{50}=0.6μM, mean diameter=43.8±2.7μm, n=6), but were unresponsive to inosine. Theo caused a rightward shift of the Ado dose-response curve. The effect of Ado analogs NECA (N-ethylcarboxamidoadenosine) and R-PIA (N^6-2-phenylisopropyl adenosine) on intracerebral arterioles were tested and found to exhibit the following order of potency: NECA>Ado>R-PIA. The responses of rat intracerebral arterioles in vitro to Ado analogs and Theo are in general comparable to those exhibited by extraparenchymal vessels in vivo, and are probably mediated by the A2 receptor.

46.4

MONO-L-ARGININE-CONTAINING COMPOUNDS DILATE PIGLET ARTERIOLES VIA AN EDRF-LIKE SUBSTANCE. D. W. Busija, L. C. Wagerle, and C. W. Leffler. Univ. of TN, Memphis, TN 38163

The characteristic nonprostanoid endothelium-derived relaxing factor (EDRF) does not appear to be an important mechanism mediating responses in piglet pial arterioles. Application of mono-l-arginine-containing compounds dilates resistance vessels via production of an EDRF-like substance. We tested the hypothesis that administration of mono-l-arginine-containing compounds would dilate piglet cerebral arterioles via generation of EDRF. Arteriolar diameters were measured via intravital microscopy in 1-5 day old pigs equipped with a closed cranial window. Initial diameters were ≈ 100 μm. Responses were examined after application of cerebrospinal fluid (CSF) containing no drug and following application of 10^{-5}-10^{-2} M of l-arginine (ARG), l-arginine ethyl ester (AEE), and N-a-benzoyl-l-arginine (NBA). The dose needed to elicit significant dilation was 10^{-5} M for NBA, 10^{-4} M for AEE, and 10^{-2} M for ARG. Maximal responses were 27 ± 6% for AEE (n = 9), 27 ± 4% for NBA (n = 6), and 17 ± 4% for ARG (n = 6). Coadministration of methylene blue (10^{-4} M) blocked dilation to 10^{-3} M AEE (n = 3). However, indomethacin pretreatment (5 mg/kg) did not block dilation to AEE (n = 3). Thus, mono-l-arginine-containing compounds dilate piglet pial arterioles via an EDRF-like substance.

46.5

EFFECTS OF INDOMETHACIN ON CEREBRAL ARTERY AUTOREGULATION. Nan A. Norins & Jane A. Madden*. The Medical College of Wisconsin and V.A. Medical Center, Milwaukee, WI 53295.

Experimental studies in animals have demonstrated that i.v. administration of indomethacin constricts the cerebral microvasculature and significantly reduces cerebral blood flow. Clinically, indomethacin is currently being studied for its potential role in the prevention of neonatal cerebral intraventricular hemorrhages and in the management of strokes in the adult population. We have examined the effects of indomethacin on the response of isolated feline cerebral arteries to changes in perfusion pressure throughout the normal autoregulatory range . Approximately 8 mm long segments of feline middle cerebral arteries were mounted on glass cannulas in a chamber containing warmed, oxygenated physiological saline solution (PSS). All side branches were tied off and the vessel stretched to its approximate resting length *in situ*. Internal pressure was adjusted by raising or lowering a reservoir filled with the same PSS and connected to the inflow cannula. The vessels were observed with a video system and their diameter measured . Following a 90 minute equilibration at 100 mm Hg the vessel diameter was measuredas pressure was raised in 20 mm Hg steps from 60-140 mm Hg. As expected, vessel diameter changed little throughout this range of pressure. Exposure of the artery to indomethacin (10^{-6} M) decreased arterial diameter by approximately 5% throughout the entire pressure range. However, the ability of the artery to autoregulate at this smaller diameter was maintained. These data suggest that indomethacin effectively reduces cerebral artery diameter but does not compromise the ability of the artery to maintain a smaller diameter over the normal range of arterial pressure . However, the effect of indomethacin on cerebral artery responses to hypoxia and/or hypercapnia, which may also occur in the clinical situation, should be examined over the same pressure range. *Supported by V A Medical Research Funds.*

46.6

REGULATION OF DOG HEART CYTOSOLIC 5'-NUCLEOTIDASE ACTIVITY BY $MgCl_2$ AND ATP. A.Darvish*, J.Chakraborty, S.L. Britton, P.J. Metting. Department of Physiology and Biophysics, Medical College of Ohio, Toledo, Ohio 43699-0008.

A primary deficit in the adenosine hypothesis of coronary blood flow control is the lack of knowledge concerning the exact source of adenosine that is released in response to a reduction in the myocardial oxygen supply/demand ratio. We have purified a cytosolic 5'-nucleotidase (EC 3.1.3.5) from dog ventricular tissue that may be of pivotal importance in the formation of adenosine. The enzyme was purified utilizing high speed centrifugation, $(NH_4)_2SO_4$ precipitation, and phosphocellulose column chromatography methods. The activity of cytosolic 5'-nucleotidase was assayed by measuring the release of inorganic phosphate. Enzyme activity was greatest for 5'-AMP. The rate of AMP-hydrolyzing activity of the purified cytosolic 5'-nucleotidase was increased by increasing the concentration of AMP up to 12 mM. All previous studies of both IMP-and AMP-hydrolyzing cytosolic 5'-nucleotidases have concluded that this enzyme requires Mg^{++}. In the absence of ATP and Mg^{++}, our enzyme had no AMP-hydrolyzing activity. When ATP was present, however, cytosolic 5'-nucleotidase was active even when no $MgCl_2$ was present. At an [ATP] of 5mM, the addition of 0.25 mM and 2.5 mM $MgCl_2$ increased enzyme activity from 14 nmoles/min to 20.5 and 32.5 nmoles/min, respectively. Because the level of free Mg^{++} increases *in vivo* during myocardial ischemia and hypoxia, the activation of AMP-specific cytosolic 5'-nucleotidase by Mg^{++} may play an important role in adenosine production under these conditions.
Supported by AHA, Ohio Affiliate and NIH (HL-01515).

46.7

IN VIVO INTRAMYOCARDIAL BLOOD VOLUME IN ISCHEMIC REGIONS -- ESTIMATED USING FAST CT. Xue-si Wu*, Wolfgang J.T. Spyra* and Erik L. Ritman. Mayo Medical School, Rochester, MN 55905

A previous study (Wu et al, The FASEB J 3:A405, 1989) suggested that the fraction of myocardium that is blood (FMB) relates to myocardial perfusion (F) in that region under different hemodynamic conditions as $FMB \simeq aF^{\frac{3}{2}}$. In the present study coronary stenoses due to hollow plastic cylinders embolized into the left anterior descending (LAD) or left circumflex (LCx) artery were made in eleven dogs. These, plus a twelfth dog with no stenosis, were scanned using fast CT (DSR) during injection of Iohexol (~1mL/kg) into the aortic root. Regional F and FMB were calculated using the method of Wang et al. (IEEE Trans Med Imaging 8:70-77, 1989). Each region studied was identified as one of three groups: a control region, a region perfused by a 25-43% or by a 50-55% stenotic artery. The relationship between regional F and FMB was generated from all the dogs' data for each of the three types of regions. There is a significant difference ($P<0.05$) between any two regression lines. The values for "a" were 10.2, 11.3, 12.2 respectively. Paired t-test was done to compare the control and ischemic regions for the five dogs, which had only one artery stenosis, the "a" were 9.9±1.3 for control and 12.4±0.7 for ischemic regions ($P<0.001$). We conclude that the intramyocardial blood volume, perfused by a stenotic vessel, is increased significantly. This may mean that the functional significance of a stenosis can be evaluated with just a single resting angiographic study.

46.8

HETEROGENEITY OF INTRAMYOCARDIAL BLOOD FLOW, BLOOD VOLUME AND TRANSIT TIME-FRACTAL ANALYSIS OF FAST CT IMAGES. Nai-hua Shu* and Erik L. Ritman. Mayo Medical School, Rochester, MN 55905

The DSR, a fast CT scanner, was used to estimate intramyocardial blood volume, blood flow and tissue transit time in selected locations within the heart wall of 4 dogs using the method of Wang et al. (IEEE 8:70-77, 1989). The spatial heterogeneity of these parameters was evaluated by the fractal model $RD(m)=RD(m_0)*m^{1-D}$ (NIPS 3:5-10, 1988) for different hemodynamic states. RD=standard deviation/mean of, for instance, blood flow in all pieces of myocardium of weight m, m_0 is the mass of the LV wall and D is the fractal dimension with a value between 1.0 (homogeneous) and 1.5 (random). RD was measured from the fast CT images for between 10 mg to 10 g where the model fits the data with $r=0.974$. Using the fractal model the RD for 1 mg pieces was estimated by extrapolation.

	Flow		Blood Volume		Transit Time	
	D	RD(1mg)	D	RD(1mg)	D	RD(1mg)
C	1.178	0.46	1.168	0.41	1.024	0.042
A	1.180	0.34	1.170	0.31	1.023	0.041
P	>0.05	<0.01	>0.05	<0.01	>0.05	>0.05

C = control, A = adenosine infusion. Mean ± sd. deviation.

At the 1 mg level the heterogeneity of myocardial perfusion is matched by a comparable heterogeneity of intramyocardial blood volume and flow, both of which decrease their heterogeneity with vasodilation. However, transit time through 1 mg remained relatively homogeneous and invariate with flow.

46.9

VENTILATORY EFFECTS ON CORONARY FLOW AND CARDIAC WORK WITH HEART FAILURE. H. Veldenz*, D. Dries*, G. Djuricin*, M. LaBarbera*, P. Lamar*, M. Mathru*, and H.K. Jacobs. Loyola Med. Sch., Maywood, Il, and Hines VA Hosp., Hines, IL 60141

We tested the hypothesis that the increased blood flow required by the respiratory muscles during spontaneous breathing (SB) versus mechanical ventilation (MV) could compromise the heart if cardiac function is limited. Eight chloralose anesthetized mongrel dogs were intubated and instrumented with a left atrial cannula, a high frequency catheter transducer in the left ventricle (LV) and ultrasonic wall thickness crystals. The chests were closed and evacuated. After 30 minutes on MV, hemodynamic data were taken and 1 of 4 radiolabled microspheres was injected. SB was started and all data were taken after 15 minutes. Myocardial failure was then induced by intracoronary injection of 25 micron beads. After 45 minutes data were taken for SB in the failure mode. MV was reinstituted and data were taken 15 minutes later. Cardiac outputs were decreased and filling pressures elevated following instillation of the beads. SB diaphragmatic blood flows were increased over MV but there were no differences in these flows due to failure alone. Coronary flows were elevated with failure but there were no detectable differences between SB and MV. The LV free wall thinned and cardiac work decreased with failure but there were no differences between SB and MV. The data in this model show that the added blood supply to the respiratory muscles necessitated by SB is accommodated without detriment to the heart.

46.10

THE EFFECT OF CALCITONIN GENE RELATED PEPTIDE (CGRP) ON CORONARY FLOW AND MYOCARDIAL PRESERVATION. T. Liu*, C. Joyce*, R. Prinz*, J. X. Thomas, R. Fiscus, G. Djuricin*, M. LaBarbera*, and H.K. Jacobs. Loyola Univ. Med. Sch., Maywood, Il and Hines VA Hospital, Hines, Il 60141.

We have recently shown that CGRP, a known vasodilator, caused decreased coronary resistance but no changes in canine ventricular dynamics. We therefore tested the hypothesis that CGRP might improve coronary blood flow in the face of a lesser work demand and be beneficial in limiting a developing infarct in dogs. Ten open-chest mongrel dogs were anesthetized with chloralose (80 mg/kg), intubated and ventilated. Coronary flows were studied with radiolabeled microspheres. Acute myocardial ischemia was induced by permanently ligating the LAD below its first diagonal branch. Animals were followed for six hours, the hearts harvested and the left mains injected with microfil to demarcate those areas of the heart not at risk. A vital dye was used to delineate risk from dead areas. CGRP was given intracoronary as a 10 min. infusion at 600 pmoles/min at 1 hr post ligation. The control group received vehicle. The data show that coronary flows in those non-risk areas of the heart were significantly elevated following CGRP infusion. Areas of the heart at risk in the CGRP dogs did not demonstrate any changes in flow vs control dogs. Those portions of the heart eventually dying were statistically identical in flows and areas between groups. These results indicate that CGRP is a coronary vasodilator but does not limit infarct size.

46.11

INTRAMYOCARDIAL PUMP CONCEPT EXAMINED IN AN ANALOG MODEL OF THE CORONARY CIRCULATION. Hani N. Sabbah, Mohamed S. Hamid*, Gary W. Rankin*, Paul D. Stein. Henry Ford Heart and Vascular Institute, Detroit, MI 48202.

The concept of coronary extravascular compressive forces displacing blood retrograde toward the epicardial arteries and antegrade toward the epicardial veins during systole, "intramyocardial pump", was examined in an analog model of the coronary circulation. The left ventricular myocardium was modelled as 3 equal and parallel layers each containing arterial and venous resistances on either side of a lumped arterial and venous capacitance. Extravascular compressive forces in each layer were represented by simulated phasic intramyocardial pressure (IMP). Model solutions were obtained for 5 sequential 20% increments of systolic IMP in each layers while keeping model capacitances, resistances, diastolic IMP and coronary perfusion pressure unchanged. An increase of systolic IMP by 20, 40, 60, and 80% resulted in a stepwise decline of mean sytolic epicardial coronary arterial flow from 22.6 to 16.0, 7.7, 1.0, and -5.2 ml/min respectively. At the same time, mean systolic epicardial venous return increased from 57.7 to 70.8, 90.3, 94.6 and 101.8 ml/min respectively. These predictions are compatible with the concept of an active intramyocardial pump and are consistent with limited observations in dogs.

46.12

Coronary Microvascular Sites of α_1-Adrenergic Constriction. William M. Chilian, Susan M. Layne*. Department of Medical Physiology, Microcirculation Research Institute, Texas A&M University, College Station, TX 77843

In a previous report we failed to demonstrate α-adrenergic constriction in small coronary arterioles (<100μm in diameter), possibly due to autoregulatory escape of these small vessels. We tested the hypothesis that if autoregulatory adjustments are abolished during coronary hypoperfusion (perfusion pressure [CPP] at 40mmHg), small coronary arterioles would constrict to the α_1-adrenergic agonist phenylephrine (PE). In anesthetized open-chest dogs, coronary microvascular diameters (CMD) were measured in the beating heart using stroboscopic epi-illumination. Measurements of hemodynamics, CPP, and CMD were made during baseline conditions, intracoronary infusion of PE (0.1 and 1.0μg/min), reduction in CPP to 40mmHg, and PE during CPP at 40mmHg. Hemodynamics did not change during the interventions. Results: Constriction during PE expressed as a %Δ from baseline or during CPP-40 $\bar{x}$±SEM. *p<0.05 vs. Baseline or CPP-40.

	%Δ from Baseline		%Δ from CPP-40mmHg	
CMD	PE-0.1	PE-1.0	PE-0.1	PE-1.0
20-100μm	+3.7±1.5%	+2.3±1.9%	+1.3±1.8%	+0.5±0.9%
>100μm	-7.8±2.3%	-10.2±1.9%*	-6.8±1.2%*	-8.9±0.9%*

Coronary arterioles (<100μm in diameter) did not constrict, even when instrinsic autoregulatory adjustments were abolished. Thus, coronary microvascular α_1-adrenergic constriction occurs in large arterioles and small arteries greater than 100μm in diameter.

46.13

REGENERATION OF ASCORBIC ACID IN RAT HEART. *Ann M. Bode and Richard C. Rose. University of North Dakota School of Medicine, Department of Physiology, Grand Forks, ND 58202.

Enzymatic reduction of dehydro-L-ascorbic acid (DHAA) by dehydro-L-ascorbic acid-reductase (DHAA-R) might be an important means of conserving ascorbic acid (AA) by recycling DHAA. Tissue levels of DHAA-R may be an important determinant in resistance to free radical-induced cellular damage, especially in tissues where oxygen metabolism is of primary importance, such as the heart. The purpose of this study was to explore the possible presence and role of DHAA-R in cardiac tissue. The activity was analyzed in the 1000 xg supernatant derived from a homogenate of rat heart. The reactive factor was found to be present in the 50-70% ammonium sulfate fraction, which contained 36% of the total protein, and was retained by 12,000 MW dialysis tubing. Fractions (2 mg/ml protein) were incubated at 37°C for 15 minutes in the presence of 0.6 mM GSH, 0.2 mM NADPH, 1 mM thiourea, and varying concentrations of DHAA. Activity was dependent upon NADPH as the preferred reducing agent. Activity of the factor increased with increasing DHAA concentration and was found to be heat and acid labile and temperature and pH dependent. We therefore conclude that a factor resembling dehydro-L-ascorbic acid-reductase does exist in cardiac tissue and has a role in reducing DHAA to AA.

46.14

IGM-ANTICARDIOLIPIN-ANTIBOIDES EVOKE ENDOTHELIUM-INDEPENDENT RELAXATIONS IN ISOLATED CANINE CORONARY ARTERIES. B. Eber,* M.L. Biondi,* W. Auch-Schwelk,* P.M. Vanhoutte. Mayo Clinic, Rochester, MN 55905.

Elevated IgM- and IgG-anticardiolipin-antibodies (ACA) are associated with both arterial and venous thrombosis in humans. Experiments were designed to study the influence of these phospholipid-antibodies on vascular smooth muscle reactivity. Rings of the left descending canine coronary artery with and without endothelium were suspended in organ chambers for isometric tension recording. The IgM-ACA induced endothelium-independent relaxations in a concentration-dependent manner following contraction with prostaglandin F_2-alpha, whereas the IgG-ACA and the solvent had no effect in this respect. Indomethacin had no influence on the relaxations. Methylene blue and hemoglobin markedly inhibited the relaxations to IgM-ACA. After a wash-out period of 60 minutes, endothelium-dependent relaxations evoked by acetylcholine, bradykinin, and thrombin, and endothelium-independent relaxations to isoproterenol were not influenced by the antibodies. Thus, IgM-ACA induces endothelium-independent relaxation which may be associated with the production of cyclic GMP.

TISSUE TRANSPORT

47.1

EFFECT OF PERITONEAL FIBROSIS ON PERITONEAL TRANSPORT IN THE RAT. S. Webster, C. Huntenburg*and C. Dinarello* Baxter Healthcare Corp., Applied Sciences, Round Lake, IL

Patients on peritoneal dialysis frequently lose efficacy of dialysis due to fibrosis (PF). The present study evaluates the long term effects of inflammation due to administration of chlorhexidine (CHL) on peritoneal transport and histopathology in the rat.

CHL (0.1 mg/kg) was administered daily IP. to rats for 14 days. Peritoneal solute transport and histopathology was evaluated 2, 4, and 8 weeks post CHL treatment and compared to solute transport before and immediately following cessation of CHL injections. The results are shown as dialysate to plasma (D/P) ratios of solutes 15 min. after infusion of dialysate into the peritoneum, immediately, 4, and 8 weeks after cessation of injections.

	Time Following CHL Injections			
D/P	untreated	0	4	8 weeks
Urea	0.64 ± 0.02	0.90 ± 0.03	0.71 ± 0.05	0.58 ± 0.07
Creat	0.47 ± 0.02	0.65 ± 0.02	0.48 ± 0.03	0.45 ± 0.01

The results demonstrate a decrease in peritoneal transport following the initial inflammatory response, which correlates with the development of peritoneal fibrosis determined histologically. The gradual loss of peritoneal dialysis efficacy in patients may involve the development of fibrosis following an episode of intense peritoneal inflammation.

47.2

TRANSPERITONEAL FLUID DYNAMICS IN RABBIT LIVER. D. Negrini, C. Gonano,* M.Del Fabbro *and G.Miserocchi. Istituto di Fisiologia Umana, Università di Milano.

A small hollow capsule (0.11 cm^3) was glued to the exposed liver surface of 14 anesthetized, spontaneously breathing rabbits. The capsule was filled with homologous plasma and initially closed against a pressure transducer until an equilibrium pressure, reflecting the hydraulic pressure of the liver interstitium (Ptl), was reached. Ptl averaged 2.5±1.22 (SD) cm H_2O. Then the capsule was connected to a graduated pipette to measure fluid flow through the peritoneal liver surface at different capsular pressures. The slope of the capsular flow vs capsular pressure regression was the filtration coefficient of the peritoneum-hepatic sinusoids interface. From the surface area of the capsule we calculated an average hydraulic conductivity of the interface of $6.1 \cdot 10^{-3} \pm 5 \cdot 10^{-3}$ (SD) ml/(h·cm H_2O·cm^2). The estimated filtration from hepatic sinusoids into the peritoneal cavity at physiological peritoneal liquid pressure, was about 0.5 ml/h.

47.3

IMAGING EVALUATION OF ALTERED LYMPHATIC DRAINAGE BY "PASSIVE" TECHNIQUE OF MEASURING RETENTION OF RADIOPHARMACEUTICALS SUCH AS Tc-99m-DIPHOSPHONATE BONE AGENTS. M.K. Karimeddini* and R.P. Spencer. Univ. Massachusetts Medical Center, Worcester, MA 01655 and Univ. Connecticut Health Center, Farmington, CT.

The usual radionuclide approach to determining patency of lymphatic pathways in the extremities is "active" in that labeled particulates are injected subcutaneously and their disappearance followed (and pathways delineated if possible). However, a more "passive" approach may be possible, using the clearance of intravenously administered radiopharmaceuticals from a region. It has been well recognized that, following radical mastectomy, a small fraction of the women will have swelling of the ipsilateral arm (presumably due to lymph-edema). On Tc-99m-diphosphonate bone scans, the soft tissue can be noted to be prominent. We have found that there are likely 2 phenomena involved: volume of tissue affected (V) & uptake per unit of tissue (U). Thus, the content of retained activity (C) is given by: $C = V.U$. In early (recent onset) lymphedema of the arm, C appears directly proportional to V; that is, uptake per unit of soft tissue is no different than the other extremity. However, it may be that U increases with time, due to fibrosis and changes from inadequate drainage. In the lower extremities, such as following lymph node resection for melanoma, U may be playing a more important role, likely related to gravitational effects.

47.4

OXYGEN MICROELECTRODE TECHNIQUE FOR EVALUATING CONCENTRATION DEPENDENT METABOLISM IN STENOSED VASCULAR WALLS. Donald G. Buerk, Kendra Gealow* and Stephen E. Dubin*. Drexel University, Philadelphia, PA 19104.

Recessed cathode (Whalen-type) PO_2 microelectrodes with tips < 5 μm were used to study vascular wall O_2 metabolism in isolated, perfused rabbit abdominal aortas (n = 16) using a new experimental technique. The vessels were stenosed with a tantalum clip implanted 3 to 6 months prior to the study. After microelectrodes were positioned into the wall at the location of the minimum PO_2 during steady flow conditions, the rate of O_2 disappearance (dPO_2/dt) was measured by stopping luminal perfusion. The metabolic rate can be calculated from either measurement. The minimum PO_2 was 11.5 ± 3.0 (SE) % lower ($p < 0.01$) immediately downstream in the stenosis compared to the uninjured wall far upstream. dPO_2/dt was 46.1 ± 14.8 % faster ($p < 0.005$) immediately upstream compared to the uninjured wall. O_2 disappearance curves were found to be highly dependent on O_2 concentration. Part of this dependence can be attributed to the decreasing volume of wall tissue being supplied from the lumen as perfusate PO_2 falls. After correcting for this effect from an O_2 transport model for the experiment, the effective Michaelis-Menten constants (Km) were estimated to be 4.6 and 10.9 mmHg respectively for the uninjured and stenosed wall. These data are consistent with a low O_2 affinity metabolic pathway in addition to the usual high O_2 affinity oxidative metabolism, with greater activity in the stenosis. (Supported by HL 37048 from NIH).

BODY FLUID REGULATION

48.1

EFFECT OF INFLAMMATION ON PERITONEAL TRANSPORT IN THE RAT C. Huntenburg,* S. Webster, M. Salit* and C. Dinarello*
Baxter Healthcare Corp., Applied Sciences, Round Lake, IL

Infection and inflammation may reduce the ability of the peritoneum to clear solutes and remove fluid in patients on peritoneal dialysis. These studies evaluated the effect of inflammation due to chlorhexidine (CHL) administration on rat peritoneal solute transport and lymphocyte infiltration.

Following daily intraperitoneal injections of CHL (0.1 mg/kg), rats were nephrectomized 18 hours prior to peritoneal trans-port evaluation. Under anesthesia, peritoneal and arterial catheters were implanted and dialysate was instilled into the peritoneal cavity. Samples of dialysate and blood were obtained for solute and wbc evaluations. Samples of peritoneum were evaluated for histopathology.

Solute	CONTROL	CHL
Urea (D/P)*	0.80 ± 0.02	0.93 ± 0.03
Creatinine (D/P)*	0.56 ± 0.02	0.65 ± 0.02
Glucose (D/Do)	0.47 ± 0.02	0.40 ± 0.02
Lymphocyte (%)	11 ± 3	51 ± 4

*D/P is dialysate to plasma ratio after 15 min. dwell.

The increase in peritoneal transport rate as determined by a more rapid increase in D/P values correlated with an increase in peritoneal membrane thickness shown by histo-pathology. These results help to explain the loss of ultra-filtration in patients with peritonitis since the gradient for water transport (D/Do glucose) dissipates more rapidly.

48.2

THE INCREASE IN PLASMA VASOPRESSIN ELICITED BY INTRAVENOUSLY INFUSED HISTAMINE IS NOT ATTENUATED BY SINOAORTIC DENERVATION IN CONSCIOUS DOGS. B.C. Wang, J.L. Zhu*, R.J. Leadley, Jr., J.B. Madwed, and K.L. Goetz. St. Luke's Hospital and Foundation, Kansas City, MO 64111

Intravenous infusion of histamine causes a marked increase in plasma vasopressin (AVP) which may be mediated by cardiovascular reflexes. We have previously reported that a reflex from cardiac receptors is not responsible for this increase in AVP. The present study was designed to determine whether a reflex from sinoaortic baroreceptors is required for the histamine-induced increase in AVP. Experiments were performed on intact and sinoaortic-denervated (SAD) dogs. Histamine was infused intravenously at rates of 1, 2.5, or 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min into each dog on separate days. Arterial pressure decreased in both groups of dogs, but the magnitude of the decrease was greater in SAD dogs. Heart rate increased in intact dogs but remained unchanged or decreased in SAD dogs. Histamine produced marked increases in plasma AVP in both groups of dogs; the response of the SAD dogs did not differ significantly from the response of the intact dogs. This study, along with our previous work, suggests that neither reflexes from cardiac receptors nor from sinoaortic receptors are responsible for the increase in plasma AVP induced by histamine infusion.

48.3

THE MODEST NATRIURESIS ELICITED BY LOW-DOSE ATRIAL PEPTIDE INFUSION IS NOT ATTRIBUTABLE TO OPPOSING ANTINATRIURETIC EFFECTS OF CARDIAC REFLEXES. R.J. Leadley, Jr., B.C. Wang, J.L. Zhu*, J.B. Madwed, and K.L. Goetz. St. Luke's Hospital and Foundation and University of Kansas Medical Center, Kansas City, MO 64111

Low-dose infusions of atrial peptide into conscious dogs produce only a modest natriuresis. These infusions also decrease atrial pressures, a change that conceivably could elicit a decrease in sodium excretion via an atrial receptor reflex. To determine whether such a reflex might conceal the full natriuretic potency of atrial peptide, we compared the natriuretic response to low-dose infusions of α-hANP in cardiac-denervated and sham-operated (intact) conscious dogs. After a 20-min control period, α-hANP was infused into each dog at either 12.5, 25, or 50 $ng \cdot kg^{-1} \cdot min^{-1}$ for 1 h, followed by two 20-min recovery periods. Left and right atrial pressures decreased significantly in all dogs at each rate of infusion ($p < 0.05$). Atrial peptide infusion at each rate produced an increase in sodium excretion that did not differ (n.s.) between the cardiac-denervated and the intact dogs. These results indicate that the modest natriuretic action of low doses of atrial peptide is not attributable to counteracting effects from cardiac reflexes.

48.4

Phosphodiesterase (PDE) Inhibitors Potentiate Renal Effects of Atrial Natriuretic Peptide (ANP) in Anesthetized Rats. J. Keiser, R. Weishaar, D. Taylor, Parke-Davis Pharmaceutical Research, Warner-Lambert Co., Ann Arbor, MI 48105.

ANP plays a role in regulation of sodium (Na) and fluid balance. Data suggest cGMP is the second messenger mediating ANP'S renal effects. We evaluated potentiation of the renal response to ANP by calmodulin sensitive (PDE IB) and calmodulin insensitive (PDE IC) subclasses of PDE inhibitors. Rats were anesthetized with Inactin, artery, veins and ureters cannulated. Urine volume (UV) and Na excretion ($U_{Na}V$) were determined during six 15 minutes periods. Dose response curves were constructed to the PDE 1C inhibitor M&B 22948 (M) (30-1000 ug/kg/min), the PDE 1B inhibitor TCV-3B (T) (10-300 ug/kg/min) and ANP (3-1000 ng/kg/min) in separate groups. M or T alone increased UV and $U_{Na}V$; M produced a 5 fold increase in $U_{Na}V$ while T increased $U_{Na}V$ 2 fold. In contrast, ANP increased $U_{Na}V$ 30 fold. Coadministration of ANP with M or T potentiated the $U_{Na}V$ response. Rats treated with M (30 ug/kg/min) and ANP (100 ng/kg/min) excreted 7.1 ± 1.4 uEq/min Na above control, ANP or M alone raised $U_{Na}V$ by 2.7 ± 1.1 or 0.9 ± 0.3 uEq/min, respectively. Coadministration of T (10 ug/kg/min) and ANP (300 ng/kg/min) raised $U_{Na}V$ by 17.3 ± 4.4 uEq/min. ANP or T alone raised $U_{Na}V$ by 6.2 ± 2.1 or 0.8 ± 0.4 uEq/min. Both M and T potentiated ANP responses suggesting calmodulin sensitive and insensitive subclasses of PDE are involved in regulating ANP responses.

48.5

ANTIINFLAMMATORY AND ANTIPROTEOLYTIC PROPERTY OF NEWER SUBSTITUTED 1,3,4-OXADIAZOLES. Surendra S. Parmar, Krishna Raman* and Steven K. Salzman*. A.I. DuPont Inst., Dept. of Res., Wilmington, DE 19899 and Dept. of Physiol., Univ. of North Dakota, Grand Forks, ND 58202

Antiinflammatory activity of eight 1-(4-biphenoxyacetyl)-4-substituted arylthiosemicarbazides and their cyclized 2-(4-biphenoxymethyl)-5-arylamino-1,3,4-oxadiazoles was determined by their ability to protect carrageenin-induced edema in rat paw. All thiosemicarbazides (100 mg/kg i.p.) possessed 21-67% antiinflammatory activity which decreased on cyclization to oxadiazoles (4-bromo, 4-iodo, 4-methoxy, 2-ethoxy, 4-ethoxy, or unsubstituted). Increased activity was observed during cyclization of thiosemicarbazides containing 4-chloro, 2-methoxy or 4-methoxy substituents. Maximum protection activity of 67% ($p<0.001$)was observed with 2-methoxy substituted thiosemicarbazide and its cyclized oxadiazole (76% [$p<0.001$] vs. vehicle). An increase in antiproteolytic activity was observed on cyclization with the exception of 4-bromo, 2-methoxy or 4-methoxy substituted thiosemicarbazides. Low toxicity of test compounds was reflected by high approximate LD_{50} values (700-1000 mg/kg, i.p., in mice). These results provide evidence for antiinflammatory activity of thiosemicarbazides and their cyclized 1,3,4-oxadiazoles independent of their antiproteolytic effectiveness. (Supported in part by Max Baer and Bush Developmental Grants.)

LUNG MECHANICS: GENERAL

49.1

EFFECT OF PLEURAL MEMBRANE ON THE PROPAGATION OF RAYLEIGH-TYPE SURFACE WAVES IN INFLATED HORSE LUNGS. C.-S. Man*, M. Jahed*, P.K. Bhagat* and S. J. Lai-Fook, University of Kentucky, Lexington, KY 40506.

We consider stress waves superimposed on an inflated lung at a given transpulmonary pressure (P). We model the lung parenchyma as an elastic half-space and the pleura as a taut membrane in smooth contact with the half-space. Our analysis shows that Rayleigh surface waves are weakly dispersive and there is a cutoff frequency (fo) above which no transmission occurs. The wave velocity at fo equals the shear wave velocity, $(\mu/\rho)^{1/2}$, where μ is the shear modulus and ρ the density of the half-space. fo depends mainly on T/μ, where T is the membrane tension. In 3 isolated lungs, we measured transmitted signals 20-35 cm from a surface distortion using microphones embedded in the pleura surface. The surface distortions were generated either by single frequency modulated pulses or a 150 Hz band limited signal. Surface wave velocity (Vr) versus frequency (f) was measured by transit time analysis of the filtered signals. Vr averaged 193 ± 28 (SD), 252 ± 56 and 316 ± 72 cm/s at P = 5, 10 and 15 cmH_2O, respectively. These values were consistent with a shear modulus of 0.95P. Vr increased slightly with f. Cutoff occurred above 60-100 Hz. This cutoff frequency was consistent with T values of 2500 and 10,000 dynes/cm at P values of 5 and 15 cmH_2O, respectively. (Suppported by HL 40362).

49.2

FINITE ELEMENT ANALYSIS OF REGIONAL LUNG EXPANSION IN PRONE AND SUPINE POSITIONS: EFFECT OF HEART WEIGHT AND DIAPHRAGMATIC COMPLIANCE. Sundaresh Ganesan* and Stephen J. Lai-Fook, University of Kentucky, Lexington, KY 40506.

Previous studies have shown that the vertical gradient in transpulmonary pressure (Ptp) is greater in the supine than in the prone body position. We developed a finite element model of the lung and heart to determine the relevant factors. We used a dried inflated dog lung sliced into 9 transverse sections to obtain the model's dimensions. Chest wall compliance was simulated using spring elements attached to nodes on the pleural surface. Shear modulus of the lung at FRC was 3.5 cmH_2O; Poisson's ratio was 0.4. Density of lung was 0.23 and of heart, 1 g/ml. Gravity was imposed in the appropriate direction. From the computed stress distribution, we obtained the vertical Ptp gradient by averaging the normal stresses in 3 lung sections near mid heart. For a uniformly stiff chest wall, Ptp gradient averaged 0.12 cmH_2O/cm in both prone and supine positions. When the compliance on the diaphragmatic pleural surface was increased 100 fold, Ptp gradient increased to 0.38 cmH_2O/cm in the supine position but was unchanged prone. Absence of heart weight reduced supine gradient to 0.15. Thus, both heart weight and a compliant diaphragm are needed to explain the large vertical Ptp gradient in the supine position. (Supported by HL 36597).

49.3

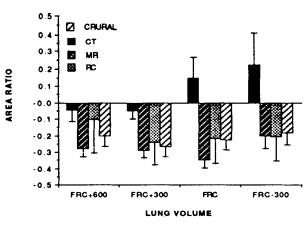
DISTRIBUTION OF OXYGEN DELIVERY (DO_2) TO RESPIRATORY MUSCLES (RM) DURING EXERCISE IN POST-PNEUMONECTOMY FOXHOUNDS. C.C.W. Hsia, J.L. Pean, S.S. Cassidy & R.L. Johnson, Jr. Dept. of Int. Med/Pulm. Research, University of Texas Southwestern Medical Center, Dallas, TX 75235-9034.

In three foxhounds after left pneumonectomy, blood flow to RM during heavy exercise were measured by standard microsphere technique. Minute ventilation ($\dot{V}_E$ in L/min), O_2 consumption ($\dot{V}_{O_2}$ in ml/min) and arterial O_2 content were simultaneously determined. DO_{2RM}(ml/min)=16.5+1.0 $\dot{V}_E$ (R=0.67) where DO_{2RM} is arterial O_2 content x RM blood flow. DO_{2RM} comprised 5.1% and 6.2% of total body $\dot{V}_{O_2}$ at rest and during exercise at a $\dot{V}_E$ of 100 L/min, respectively. Distribution of total DO_{2RM} among various RM were similar at rest and during exercise: Inspiratory muscles .55; expiratory muscles .45. Diaphragm .23 (costal .15, crural .08); transverse abdominus .07; triangularis .05; parasternals .15; levator costorum .05; scalenus .02; external oblique .11; internal oblique .08; external intercostals .09; internal intercostals .14; posterior cricoarytenoid .003. Diaphragmatic blood flow (ml/min·gm)=0.06+0.01 $\dot{V}_E$ (R=0.83). During exercise blood flow per gram of muscle to costal diaphragm is 30% higher than that to crural diaphragm. We conclude that 23% of the total and 42% of the inspiratory work of breathing is borne by the diaphragm at rest and during heavy exercise in the post-pneumonectomy foxhound. Supported by HL40070 and The Will Rogers Institute.

49.4

REGIONAL DEFORMATION OF THE CANINE DIAPHRAGM DURING MUELLER MANEUVER. J.L. Pean, C.J. Chuong, R.L. Johnson Jr. Univ. TX Southwestern Medical Center, Dept. of Int. Med/Pulm Res. and Univ. TX at Arlington, Dept. of Bioengineering, Dallas, TX 75235-9034.

Deformation of the canine diaphragm has been shown to be orthotropic, with shortening occurring along the axis of major deformation and elongation at the orthogonal direction. Dimensional changes are thus more adequately described as surface area changes. Biplane cineradiography was used to measure the area of different regions of the costal (near the central tendon (CT), in the mid region of the muscle (MR) or near the rib cage (RC)) and the crural (CRU) segments of the diaphragm of supine anesthetized dogs. The regions were delimited by radiopaque markers implanted in the abdominal surface of the diaphragm in triangular arrays. Area at peak inspiration during Mueller maneuvers performed at different lung volumes was expressed as the ratio of the area at end expiration.



At high lung volumes, CT deformed little while it expanded at lower volumes. There was no significant differences in area ratio changes among CRU, MR and RC at different lung volumes. Except for CT, changes in area ratio of the different regions of the canine diaphragm are not significantly different. (Supported by NIH-HL35914 and PHS-5-T32-HL07362).

49.5

INTRATHORACIC PRESSURE GENERATION BY THE CANINE PECTORAL MUSCLES. **SR Muza, GJ Criner, RR Ajello, R-A Zhang and SG Kelsen. Temple University School of Medicine, Philadelphia, PA.**

The mechanical action of the pectoral girdle muscles on the rib cage is poorly understood. We assessed the effect of selective electrical stimulation of the deep pectoral muscles (DP) on intrathoracic pressure (Pes) in 5 supine, anesthetized dogs. Pes was measured during supramaximal stimulation (30V) over a range of frequencies (10-80 Hz) against an occluded airway during hyperventilation induced apnea. With forelimbs held parallel to the side of the torso, increasing stimulus frequency produced curvilinear expiratory changes in Pes. Pes reached a maximum at 60 Hz. Forelimb elevation perpendicular to the torso converted DP into an inspiratory muscle. Decreases in lung volume below FRC diminished the expiratory action of the DP but augmented its inspiratory action. Elevation of lung volume above FRC had the opposite effect. These results show that the DP have both an inspiratory and expiratory action on the canine rib cage which depends upon forelimb posture and lung volume. Supported in part by a research grant from the Cystic Fibrosis Foundation.

49.6

MECHANICAL ACTION OF HUMAN RESPIRATORY MUSCLES INFERRED FROM FINITE ELEMENT ANALYSIS. S.H. Loring, J.A. Woodbridge*. Respiratory Biology Program, Harvard School of Public Health, Boston, MA 02115.

We used a commercial finite element analysis program to investigate the action of respiratory muscles on the human rib cage. Geometrical measurements of a cadaver were made with a 3-dimensional digitizing device. We digitized skeletal elements, internal and external intercostal muscles and parasternal muscles. The orientation and position of other respiratory muscles were obtained from published material. Measurements of costovertebral joint stiffness and material properties of cartilage and bone were incorporated in the model. Muscle forces were simulated by applying equal and opposite forces to adjacent ribs with orientations and at positions determined from muscle geometry. The magnitudes of muscle forces were estimated from measurements of muscle cross-sectional dimensions and published length-tension characteristics of respiratory muscle. Displacements of the thorax caused by respiratory muscle action can be readily simulated and observed. Intercostal muscle action appears consistent with conventional wisdom and the analysis of Hamberger. "Bucket-handle" and "pump-handle" motions of the ribs can be attributed to particular respiratory muscles. Finite element analysis, when combined with accurate geometrical and mechanical data, can be a useful tool in respiratory mechanics. (Supported by NIH grant HL33009).

49.7

ABDOMINAL COMPLIANCE DETERMINES DISTRIBUTION OF DIAPHRAGMATIC VOLUME DISPLACEMENT. H. Knight*, W. M. Petroll*, and D. F. Rochester. Univ. of Virginia, School of Medicine, Charlottesville, VA 22908

The action of the diaphragm upon the abdomen and the rib cage is influenced by the compliance of the chest wall structures. Descent of the diaphragm results in both outward displacement of the abdominal wall and expansion of the lower rib cage. We hypothesized that the volume displaced by the diaphragmatic dome (Vdi) during active respiration would result in volume displacement of the abdominal wall (ΔVab) in proportion to the passive compliance of the abdomen. In 5 supine, apneic dogs the passive compliance of the abdominal wall was calculated as the change in abdominal volume (calibrated Respitrace®) over the change in gastric pressure (ΔPga) during passive inflation. Compliance ranged from 17.0 - 70 cc/cm H_2O (mean = 47). During spontaneous tidal breathing, Vdi was calculated from measurements made on recorded fluoroscopic images of the diaphragm dome at FRC and end-inspiration. The measurements of dome dimensions and descent were employed in a previously described model (*Physiologist* 31:A65, 1988) to evaluate Vdi. ΔVab during tidal breaths was measured by the Respitrace®. Four tidal breaths in each animal were analyzed. Vdi always exceeded ΔVab but ΔVab/Vdi varied significantly between dogs (range .32 - .69, mean = .54). ΔVab/Vdi was positively correlated with the passive compliance of the abdominal wall ($R = .97$, $p < .05$). ΔVab/Vdi was inversely related to the inspiratory change in Pga ($R = .82$). When ΔVab/Vdi is small, relatively larger proportions of Vdi are directed toward lower rib cage expansion. This appears to occur when the abdominal wall is less compliant and larger increments in Pga occur. We conclude that the distribution of the volume displaced by the diaphragm is importantly dependent upon the compliance of the abdominal wall. Inspiratory change in intra-abdominal pressure may underlie the greater displacement of the lower rib cage seen when the abdominal wall is less compliant through the costal diaphragm's insertional and appositional actions.

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49.8

DIAPHRAGMATIC ZONE OF APPOSITION (ZAP) IN THE DOG. **Susan S. Margulies and Joseph R. Rodarte. Mayo Foundation.,Rochester, MN 55905 and Baylor College of Medicine, Houston, TX 77030.**

We determined the shape and area of the diaphragmatic ZAP in 6 paralyzed, anesthetized beagle dogs (8-11.5 kg) at total lung capacity (TLC), 1/2 inspiratory capacity (IC), 1/4 IC, functional residual capacity (FRC), and residual volume (RV) in the prone and supine (P&S) postures. To identify the caudal extent of the ZAP, 17 lead beads were sutured to the diaphragm around the ring of insertion. One week later, the dogs' lower thoraces were scanned in the Dynamic Spatial Reconstuctor (DSR). The coordinates of the lead markers were identified (±1.4 mm), and the cephalad edge of the ZAP was digitized in 30-40 1.4mm-thick sagittal and coronal slices in each DSR image. We interpolated the DSR data to find the position of the top and bottom of the ZAP every 5° around the thorax, and calculated the distribution of height and area of the ZAP and the total area of apposition (TAA). The ZAP increased as lung volume decreased and was largest at the lateral extremes of the rib cage. TAA did not change significantly with posture, but the ZAP in the ventral region was smaller in the supine posture. We measured the surface area of the rib cage (SARC) above the ZAP in both postures in 6 other beagles of similar stature scanned previously in the DSR. Combining these measurements with data from this experiment, we estimated total rib cage area (SARC + TAA) and calculated the portion of the rib cage covered by the ZAP as a percentage of the total rib cage area at FRC:

Posture	TLC	1/2 IC	1/4 IC	FRC	RV
Prone	9.4	15.3	20.2	24.4	33.0
Supine	9.5	16.3	19.5	22.7	28.8

Supported by HL 04664, HL 21584,and HL 07222.

49.9

PLEURAL LIQUID PRESSURE IN LATERALLY RECUMBENT RABBITS R. L. Wardle*, L.M. Tobin*, V.P. Wright* and L.E. Olson. The Ohio State University, Columbus, OH 43210-1092.

Volume is reduced in the dependent lung compared to volume in the nondependent lung in laterally recumbent animals. We measured pleural liquid pressure (Ppl) using the rib capsule technique (JAP 59:597, 1985) in 9 pentobarbital-anesthetized, laterally recumbent, spontaneously ventilating rabbits to determine if pleural liquid pressure correlated with the observed regional differences in volume. A liquid-filled capsule was placed in the fifth rib of either the right (n = 4) or left (n = 5) chest. Ppl was measured at end expiration after several large inflations when the rabbits were in right and left lateral recumbency. Capsule position relative to lung height was determined from radiographs. Measurements of Ppl were repeatable in each body position. Placement of the capsule into either the right or left chest did not influence the results. Results (mean ± SD) follow: * = significant difference at $P < 0.05$ by paired *t* test.

Capsule Position	Ppl (cm H_2O)	% Lung Height
nondependent	-3.35 (1.29)	86.1 (8.59)
dependent	1.36 (1.14)*	2.1 (6.30)*

We conclude that there is a vertical gradient in pleural liquid pressure in laterally recumbent rabbits. (Supported in part by HL38243 and HL02122)

49.10

DEFORMATION OF RIB CAGE BY LOCALLY APPLIED PRESSURE. W.A. Whitelaw*, J. Evans, R. Palmer and K. Rimmer. University of Calgary, Calgary, Alberta.

Activity of respiratory muscles is often deduced from the changes in chest wall shape that they produce. In addition to uniform expansion, muscles can cause changes in the shape of transverse sections of the rib cage and abdomen. To estimate the forces needed to do this, we compressed the lateral or AP axis of the rib cage in normal men. Subjects lay relaxed on their side (or back) on a rigid surface. Vertical forces from zero to 6 x 10^5 dynes (equivalent to 100 cm H_2O applied to the larger disc) was applied to the ribs (or sternum) by discs 2 to 4 cm in diameter. The resulting displacement in the axis of the applied force was measured with magnetometers. After an initial phase due to indentation of soft tissues, displacement was linear up to the maximum force used. Compliance to lateral compression was greatest in the free part of the lower rib cage. Lateral compression produced almost no complementary expansion of AP diameter and vice versa. Forces applied locally move the rib cage locally and must change the cross sectional area to a squarer shape by bending the chest wall. The normal movement of the rib cage in respiration therefore depends on wide distribution of the applied force rather than on the tendency of the passive rib cage to resist distortion from its elliptical shape. Changes in shape of cross section of the rib cage may prove sensitive indicators of muscle action.

49.11

EXPIRATORY MUSCLE USE IN PRONE ANESTHETIZED DOGS. G.A. Farkas, M.A. Schroeder, and A. De Troyer. Thoracic Diseases Research Unit, Mayo Clinic, Rochester, MN 55905.

The expiratory muscles play a major role during breathing in head up dogs (J Appl Physiol 64:1060, 1988). Their role in the prone posture, however, is not known. Ten anesthetized, spontaneously breathing animals were attached to a specially designed frame, which allowed smooth changes in posture from supine to prone or vice versa. A change from supine to prone elicited an increased expiratory activation of the triangularis sterni (TS) in all, of the external oblique (EO) in six, and of the transversus abdominis (TA) in eight animals. Vagotomy (vgx) eliminated the postural response of EO and TA but not the response of TS. When the amount of EMG activity was expressed as a percent of that recorded supine during breathing with 25 cm H_2O PEEP, results (mean ± SE) were as follows.

	Supine	Prone Control	Prone Post-Vgx.
TS	17.2 ± 3.2*	39.1 ± 6.4	28.9 ± 5.4
EO	0*	8.6 ± 3.7	0.4 ± 0.4*
TA	5.7 ± 3.0*	27.9 ± 7.4	3.9 ± 2.6*

*Statistically different from prone control ($p<0.05$ or less)

We conclude that in anesthetized dogs adoption of the prone posture promotes increased activation of the expiratory rib cage and abdominal muscles. The abdominal component, but not the rib cage component, depends largely on vagal mechanisms. (Supported by grant HL21584).

49.12

KONNO-MEAD (KM) TYPE UNIDIMENSIONAL MAGNETOMETERS (UNI-MAGS) DO NOT PROVIDE VECTOR ANALYSIS OF BODY-SURFACE DISPLACEMENTS. Sharon Levy, Joseph Michels*, David Henson, Dennis Silage*, and Sanford Levine. VA Medical Center & Medical College of PA, Phila., PA 19104.

To illustrate this problem, we evaluated the ability of KM Uni-mags to discriminate between on-axis and off-axis movements. At an anteroposterior (AP) on-axis displacement of 20 cm, we varied the lateral off-axis displacement from 0 to 20 cm. In the table below, we present the lateral offsets, the radial (R) distance between the origin and off-axis displacements, the uni-mag measurements and the % error defined as (R -[Uni-mag])/R times 100.

Lateral (cm)	R (cm)	Uni-mag (cm)	% Error
0	20.0	20.0	0
5	20.3	20.6	2
10	21.8	22.4	2
15	24.1	25.0	4
20	27.7	28.3	2

Similar data were obtained with vertical displacements as well as on-axis distances from the origin of 30 and 40 cm. These results demonstrate that the uni-mag responds to some aspect of the magnetic field which is quantitatively similar to the radial distance from the origin. However, since the uni-mag does not discern AP, lateral and vertical components of R, 3 dimensional magnetometers provide more information regarding body surface displacements.

49.13

THE INTERPULMONARY DISTRIBUTION OF PLEURAL PRESSURE DURING SINGLE LUNG INFLATION. R. Hubmayr, S. Marqulies, S. Nelson and M. Schroeder. Mayo Foundation, Rochester, MN, 55905

We tested the hypothesis that unilateral lung inflation (ULI) alters the interpulmonary distribution of pleural pressure (Ppl). Five dogs and 4 baboons were anesthetized supine and intubated with a divided airway. Right and left lung pressure/volume curves were measured by inflating both to a common airway pressure (Pao) while esophageal pressure was used to estimate changes in Ppl (ΔPpl). One lung was then inflated to 70% TLC with the other held at constant volume. The change in airway occlusion pressure served as estimate of ΔPpl within the contralateral chest (ΔPpl_c). ΔPpl of the inflated lung (ΔPpl_i) was calculated from its compliance, volume and Pao. In dogs, there was no significant difference between ΔPpl_i and ΔPpl_c during ULI (ΔPpl_i - ΔPpl_c = 0.4 ± 0.8 cm H_2O; $p > 0.1$). In contrast, in baboons ΔPpl_i exceeded ΔPpl_c by 1.3 ± 0.7 cm H_2O ($p < 0.05$). To evaluate the contributions of pressure transmission pathways other than the mediastinum, experiments were repeated after sternal fixation (eliminating the rib cage interdependence pathway) and after laparotomy (eliminating coupling through abdomen). These interventions had no effect on the transmission of Ppl in either species. We conclude that in patients following single lung transplantation differences in lung surface pressure may also affect the interpulmonary ventilation distribution. Supported by HL 38107.

49.14

COMPARISON OF BRONCHODILATOR DELIVERED BY METERED DOSE INHALER VS NEBULIZER IN INTUBATED PATIENTS. H. Patel, P. Gay, S. Nelson*, B. Gilles* and R. Hubmayr. Mayo Foundation, Rochester, MN 55905

We compared metered dose inhaler (MDI) and nebulizer (NEB) delivery systems in a single blind, randomized cross-over design by plotting the respiratory system recoil pressure/expiratory flow curves in 18 intubated patients with airways obstruction. Airway pressure and flow were measured during stepwise deflations of the relaxed respiratory system (interrupter technique). The improvement in average iso-recoil flow ($\dot{V}_{iso}$) at recoil pressures between 6 and 10 cm H_2O served as the index of bronchodilator response. Treatment A consisted of Albuterol 270 mcg (3 puffs MDI) while treatment B utilized nebulization of a 3 ml solution containing 2.5 mg of Albuterol. There was no difference in baseline $\dot{V}_{iso}$ before either treatment (A: 0.33 ± 0.2; B: 0.28 ± 0.18 l/sec). In 15/18 patients $\dot{V}_{iso}$ increased after MDI (mean $\Delta\dot{V}_{iso}$ = 0.10 ± 0.12 l/sec; $p \leq 0.05$). In 17/18 patients, $\dot{V}_{iso}$ increased after nebulizer therapy (mean $\Delta\dot{V}_{iso}$ = 0.10 ± 0.09 l/sec; $p \leq 0.05$). Responses were not different between the treatment arms and there was no significant order effect. We conclude that bronchodilator therapy with MDI or NEB are equally effective in improving expiratory flow in intubated patients. The reduced time and cost per MDI treatment (approximately 1/3) justifies their use in intubated patients. Supported by HL 38107.

49.15

O2 EFFECT ON CARDIORESPIRATORY (CR) RESPONSES AND O2 COST OF VENTILATION (COV) IN HYPERCAPNIC AND NORMOCAPNIC COLD. E Mannix*, I Dowdeswell*, S Carlone*, P Palange* and M Farber*. (Spon:J Williams) VAMC,Indpls, IN 46202 and Univ Rome, Italy.

Cardiorespiratory responses to O2 in COLD are variable and may be affected by hypercapnia. O2 lowers airways resistance, a determinant of the high COV in COLD, but the effect of O2 on COV has not been examined. We studied 2 groups of COLD patients (GPI-Normocapnic (n=10): PO2=64±4mmHg; PCO2=40±1; FEV1= 1.2±0.1L; pH=7.39±0.01 and GPII-Hypercapnic(n=10): PO2=48±2; PCO2=59±3; FEV1=0.8±0.2; pH=7.38±0.01) on air and 30% O2, at rest and submax exercise (EX). Results(m±SE;*$p<.05$) for GP II:

	VO2(ml/min)		VE(L/min)		HR(bpm)		CO(L/min)		SV(ml/b)	
	AIR	O2	AIR	O2	AIR	O2	AIR	O2	AIR	O2
REST	300	258*	9.3	8.0*	102	94*	6.0	5.3*	62	58
	26	16	0.8	0.6	5	4	0.5	0.6	6	6
EX	667	737	18.6	16.5*	130	120*	10.1	9.0*	84	79
	72	84	3.0	2.9	8	6	0.8	0.8	9	8

In GPI only EX VE fell with O2:23.4±3.1 to 21.8±2.7*. The O2 effect on COV was studied in 5 from each group with 7% CO2. O2 lowered COV:GPI=17.9±2.4 to 11.2±2.5*ml O2/L VE and GPII=14.8± 1.7 to 7.2±1.3*. Correlations were found between pH and the decreases in REST VE and EX HR,air to O2($r=-0.86,-0.76,p<.01$). Multiple regression revealed pH had the greatest influence on the CR variables. Conclusion: 1)CR responses to O2 are different in hyper and normocapnic COLD and appear to be influenced by pH; 2)O2 lowers COV comparably in both groups, irrespective of the level of respiratory failure.

49.16

REGIONAL METABOLIC DIFFERENCES IN THE RAT DIAPHRAGM. Scott Powers, J. Lawler, D. Criswell, H. Silverman, H.V. Forster, S. Grinton, and D. Harkins. Center for Exercise Science, University of Florida, Gainesville, FL 32611

This study characterized the biochemical properties of the rat diaphragm by measuring the activities of selected Krebs cycle and glycolytic enzymes. The diaphragm was removed from 10 female Sprague-Dawley rats (180 days/old) and dissected into five discrete anatomical regions: 1) crural (region 1); 2) left posterior costal (region 2); 3) left anterior costal (region 3); 4) right anterior costal (region 4); and 5) right posterior costal (region 5). Sections were assayed for total protein concentration, and the activities of succinate dehydrogenase (SDH, EC 1.3.99.1) isocitrate dehydrogenase (ICDH, EC 1.1.1.42), and lactate dehydrogenase (LDH, EC 1.1.1.27) were determined. Region 1 was significantly lower($P<0.05$) than regions 2-5 in SDH and ICDH activity and total protein concentration. In contrast, regions 2-5 did not differ ($P>0.05$) in protein concentration or SDH and ICDH activity. LDH activity did not differ significantly ($P>0.05$) between any region. We conclude that the crural region of the rat diaphragm differs in oxidative capacity from the costal regions and that the costal regions appear homogenous with respect to oxidative properties. Investigators using a rodent model to study diaphragmatic plasticity should consider the oxidative heterogeneity of the diaphragm when designing experiments.

49.17

RESPIRATORY SYSTEM IMPEDANCE AT NORMAL BREATHING FREQUENCIES AND VOLUMES AND DURING SIMPLE MANEUVERS. G.M. Barnas, P.J. Mills*, C.F. Mackenzie*, W.L. Sexton, P.C. Imle* and J.W. Baptiste*. University of Maryland, Baltimore, MD 21201 and K.C.O.M., Kirksville, MO 63501.

We calculated respiratory system resistance (R_{rs}) and elastance (E_{rs}) from pressure and flow at the mouth in 5 seated subjects relaxed at FRC during sinusoidal volume forcing (250, 500 and 750ml) at 0.2, 0.4 and 0.6 Hz. We also measured R_{rs} and E_{rs} at 0.4 Hz (500ml) during various simple maneuvers. During relaxation, R_{rs} was 3.3 $cmH_2O/l/s$ ($\pm$ 1.0 S.E.; N=33) at 0.4 Hz-500ml; it decreased 10 to 30% in the measured frequency range, depending on volume. R_{rs} decreased by 25% with increasing volume at 0.2Hz but only slightly at the higher frequencies. E_{rs} was 9.4 $\pm$ 0.3 cmH_2O/l at 0.4 Hz-500ml; it increased by about 25% in the measured frequency range and decreased about 20% with increasing volume. Both R_{es} and E_{rs} roughly doubled during leg lifts, torso rotation, lifting a 10 kg weight and isometric arm tension. We conclude that R_{rs} and E_{rs}: 1) show frequency and volume dependences in the range of normal breathing; and 2) increase in parallel when the respiratory muscles are used to perform non-respiratory acts.

49.18

RESPIRATORY MECHANICS DETERMINED BY FORCED OSCILLATIONS THROUGH AN ALVEOLAR CAPSULE. **J.H.T. Bates and S. Filiatrault*. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, H2X 2P2, Canada.**

By measuring flow at the airway opening and alveolar pressure at a number of lung surface sites using the alveolar capsule technique, we can assess how regional time-constants of the lung are affected by bronchoconstrictor drugs. While this approach yields information regarding changes in the ratio of regional resistance (R) and elastance (E), so far it has not been possible to assess the changes in R and E independently because the flows into each lung region have not been measured individually. We have developed a device for applying forced oscillations in flow to the lungs through an alveolar capsule. The device is a miniature version of that used by Jackson and Vinegar (J. Appl. Physiol. 47:462-467, 1979) to test the frequency responses of transducers, and consists of a small speaker (1 cm diameter) either side of which is small chamber. Movement of the speaker produces pressure changes in one of the chambers that are then related to volume changes in the other chamber which is connected to the alveolar capsule. The device allows us to apply a broadband flow signal (frequency content 0-50 Hz) to the lung through the capsule while simultaneously measuring the pressure in the capsule. Because we know the local flow we can infer the local mechanical properties of the lung region to which the capsule is attached. (Supported by M.R.C. Canada.)

49.19

RESPIRATORY MECHANICS IN THE RAT. **D.H. Eidelman, P. Saldiva*, M. Ludwig, J.H.T. Bates, J. Milic-Emili and W. Zin*. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, H2X 2P2, Canada.**

We wished to evaluate the contribution of tissue viscoelastic phenomena to pulmonary resistance (R_L) in the rat. Flow interruptions were performed in 8 paralyzed, open chested Long-Evans rats ventilated with a constant flow ventilator at 0.5 Hz. Tracheal pressure (Ptr), alveolar pressure (Palv) measured with an alveolar capsule, and flow ($\dot{V}$) were measured during inspiratory occlusions performed at 4 flow values (6,8,10,12 $ml.s^{-1}$) and 4 tidal volumes (0.5, 1, 2, 3 ml). We defined ΔPinit as the rapid drop in Ptr upon occlusion, ΔPdif as the more gradual pressure change after occlusion, ΔPmax as the sum of ΔPinit and ΔPdif and ΔPtis as the pressure change in Palv after occlusion. By dividing each of the above by the flow just prior to occlusion we obtained Rinit, Rdif, Rmax and Rtis, respectively. We found that Palv was identical to Ptr following occlusion confirming measurement of alveolar pressure. Rinit was unaffected by volume or flow. Rmax increased with volume but did not change significantly with flow. Rtis was not significantly flow dependent, but increased with increasing volume from 44% to 74% of Rmax (at $\dot{V}$=8 $ml.s^{-1}$). Static and dynamic elastances did not vary significantly between volumes and flows. These results demonstrate that tissue viscoelastic properties are an important determinant of R_L. (Supported by the Quebec Thoracic Society and the Banting Foundation.)

49.20

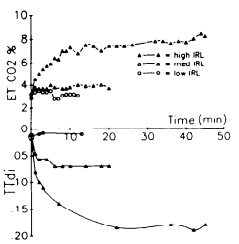
RECURSIVE LEAST-SQUARES ESTIMATION OF TIME-VARYING RESPIRATORY PARAMETERS. **A-M. Lauzon* and J.H.T. Bates. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, H2X 2P2, Canada.**

We have developed a recursive technique to follow time-variations of respiratory mechanics. A recursive least-squares method fits the equation $Ptr=EV+R\dot{V}+K$ to measurements of tracheal pressure (Ptr) and Flow ($\dot{V}$). V is obtained by numerical integration of $\dot{V}$. V usually exhibits significant drift which is corrected for prior to estimation of parameters as follows. The mean of $\dot{V}$ (i.e. the offset in $\dot{V}$) is calculated recursively and subtracted from $\dot{V}$ prior to integration. The least-squares estimator then recursively updates the parameters R, E and K as each set of measurements is obtained. A variable forgetting factor, which reduces the memory length of the estimator when the residuals increase, is incorporated into the algorithm to allow rapidly varying parameters to be tracked. The recursive technique was tested on simulated noisy data where it adequately followed a 5-fold increase in R and a 2-fold increase in E occurring over 10 sec. In two anesthetized, paralyzed, tracheostomized dogs challenged i.v. with a bolus of methacholine (approximately 13 mg/kg), a 7-fold increase in R and a 2-fold increase in E over 20 sec were observed. Similar findings were obtained in cats. These results demonstrate that our recursive technique is able to track rapid changes in respiratory mechanical parameters during bronchoconstrictor challenge. (Supported by M.R.C. Canada.)

49.21

THE LIMIT OF DIAPHRAGM ACTIVATION IN SPONTANEOUS BREATHING. J.M. Walsh, S. Romano*, A. Comtois, E. Goldman* and A. Grassino. Meakins-Christie Labs, McGill University and Notre Dame Hosp., Montreal, Quebec.

We examined the time-tension index (TTdi) resulting from the application of three levels of inspiratory resistive loading (IRL) (approx. = 40, 80 and 140 cm H2O/lit/sec). 8 mongrel dogs were lightly anesthetized with ketamine. Following the application of IRL, the TTdi reached a plateau level proportional to the level of IRL (0.04, 0.10 and 0.18 respectively). The highest level of IRL produced a TTdi which is felt to be the threshold for the development of diaphragmatic fatigue. Diaphragmatic EMG (crural and costal) showed no signs of fatigue (i.e. decrease of center frequency) at the plateau levels of TTdi. This occurred despite significant elevations of PaCO2 for the second and third IRLs (mean elevation = 150% and 230%). Further increases of the IRL beyond the third IRL resulted in no further increases of TTdi and was associated with continuous rise in PaCO2 (to levels exceeding 150 torr) followed by a decline in the TTdi as the pH fell below 6.9. The findings are consistent with the hypothesis that in the anesthetized dog, the central respiratory controller responds to the application of IRL with increased diaphragm acitivation limited at a level of TTdi beyond which diaphragmatic fatigue would develop. This represents the avoidance of diaphragmatic fatigue at the cost of respiratory failure (i.e. CO2 retention).



49.22

PULMONARY FUNCTION IN SPINAL RATS. R.F. Taylor. Center for Medical Education, Indiana University School of Medicine, Ball State University, Muncie, IN 47306 and Dept. Physiology, Oral Roberts University School of Medicine, Tulsa, OK 74137

Pulmonary mechanics were measured in chloralose, anesthetized rats using a partial body flow plethysmograph. Respiratory flow was measured with a pneumotach and a differential pressure transducer. The flow signal was integrated to yield tidal volume (TV). Transpulmonary pressure (P_{tp}) was derived by subtraction of esophageal pressure (P_{es}) from atmospheric pressure via a fluid-filled differential pressure transducer. Flow, volume and Ptp were used to calculate resistance (R) and compliance (C) using the method of Amdur and Mead (1958). Signals were displayed on a Grass Instruments 8 channel polygraph and recorded on tape for additional data analysis. Respiratory frequency (f), and minute ventilation (V_E) were obtained directly from the polygraph recordings. After complete spinal cord transection at C-6, pulmonary resistance decreased from a mean of 0.439$\pm$0.027 to 0.252$\pm$0.152 and compliance increased from 0.392$\pm$0.009 to 0.615$\pm$0.118. Respiratory frequency decreased by 31%. There was a corresponding decrease in Ve but no change in TV. Electromyograms of intercostal, diaphragm and abdominal muscles indicated a redistribution of respiratory muscle control which may account for the observed changes in pulmonary mechanics.

49.23

TOTAL PARENTERAL NUTRITON DOES NOT ACCELERATE DIAPHRAGM DEVELOPMENT IN PREMATURE BABOONS L.C. Maxwell, T.J. Kuehl*, R.J.M. McCarter, D.R. Gerstman*, R.A. deLemos. Univ. TX Health Science Center and SW Foundation for Biol. Research, San Antonio, TX.78284

Using baboons delivered by hysterotomy (gestational age 140 days), we tested the hypothesis that improved post-delivery nutrition accelerates development of diaphragm muscle (DPH). For 10 days in ventilated baboons, we gave parenteral nutrition containing glucose, electrolytes and water (GLU) or total parenteral nutrition (TPN) consisting of lipids, amino acids, glucose, vitamins and electrolytes. The GLU group had 3 females and four males; the TPN group had 4 females and 3 males. At sacrifice, samples were taken from the dorso-lateral (DL) and ventro-lateral (VL) costal DPH for histochemical studies of mean fiber area (MFA) and percentage of fiber types. A bundle was removed for determination of isometric twitch (Pt) and tetanic (Po) tension (normalized for cross-sectional area of the isolated bundle), time to peak twitch tension, half-relaxation time, force frequency relationship and fatigability. No effect of sex or nutritional treatment on contractile properties was found. Differences between sexes and amongst muscle sites, but no effect of nutrition, were observed for histochemical characteristics. A lower percentage of Type IIa fibers and greater MFA of Type IIa and IIc fibers were found in VL diaphragm compared to DL diaphragm in females or either site in males. Larger fibers in DPH of females compared to males suggests stronger DPH in females. An earlier growth of Type II fibers in females than males could contribute to a better outcome for female than male human premature infants with hyaline membrane disease. (Supported by NIH grant HL 38427.)

THE PULMONARY CIRCULATION: NEW INSIGHTS

50.1

BRIEF PERIODS OF STOPPED BLOOD FLOW INCREASE VASCULAR RESISTANCE IN ISOLATED, PERFUSED RAT LUNG. G. Yang* and J. Bhattacharya. St. Luke's-Roosevelt Hosp. Ctr., Depts. Physiol. & Med., Columbia Univ., New York, N.Y. 10019.

We investigated the effect of stopping blood flow for short periods in the isolated, blood perfused rat lung (Sprague-Dawley, 529±23 g). In 8 experiments, we held lungs at constant inflation pressure of 3 cmH_2O. Then we perfused them with heterologous rat blood which we diluted (hematocrit = 25%) with albumin solution (HSA, NYBCEN). During perfusion, we held constant pressures throughout at 11 cmH_2O in the pulmonary artery and 4 in the left atrium. After 15 min of baseline, we stopped flow for 20 min, then reperfused for 20 min. During stopped flow, we measured isogravimetric pressure which was 5.5±.7 cmH_2O at baseline. We repeated these paired periods of stopped flow and reperfusion 3 times. Blood flows (ml/min) at the respective perfusion periods are shown in the table (mean±S.D.).

Period	Baseline	1	2	3
Flow	13.2±3.1	11.9±2.9	9±2.8	7.7±3.2

With each successive reperfusion period flow decreased progressively ($p<0.05$), but isogravimetric pressure did not change. Therefore repeated, brief periods of stopped flow irreversibly increased pulmonary vascular resistance but did not affect microvascular permeability. We attribute the increase of resistance to settling of red cells during stopped flow (Support:HL 36024, HL 01696, AHA 860681).

50.2

EFFECT OF AIRWAY PRESSURE ON PULMONARY CAPILLARY TRANSIT TIME IN RABBITS. P. M. Wang,* Q. H. Yang* and S. J. Lai-Fook. University of Kentucky, Lexington, KY 40506.

In 3 anesthetized, paralyzed rabbits, mechanically ventilated with 100% O_2 in the left lateral position, a thin transparent parietal pleural window was made in the 6-7th intercostal space by dissection of intercostal muscle and endothoracic fascia. During apnea at airway pressures (Paw) between 0 and 20 cmH_2O, we injected a bolus of 0.25 ml 0.5% fluorescein sodium into the right ventricle. Injection time was 0.2 s. Transmission of the dye through pulmonary subpleural microvessels beneath the pleural window was recorded on video tape via a fluorescent video-microscopy system. Dye dilution curves of an arteriole and venule were constructed by gray scale frame-by-frame analysis of the digitized video signals every 1/30 s. We obtained transit time from the time weighted averages of the dye dilution curves. We used the Kontron Image Processing System for the data analysis. Transit time from the right ventricle to the subpleural arterioles averaged 2.8 ± 0.64 (SD) s at 0-5 cmH_2O Paw and increased to 8.9 ± 4.8 s at 15-20 cmH_2O Paw. Capillary transit time from the subpleural arterioles to the subpleural venules averaged 0.59 ± 0.30 s at 0-5 cmH_2O Paw and increased to 2.2 ± 0.84 s at 15-20 cmH_2O Paw. The increased transit times were due to a 50% decrease in cardiac output (thermal dilution) from 90 ± 26 to 44 ± 15 ml/min/kg. (Suppported by HL 36597).

50.3

BRONCHIAL BLOOD OXYGEN TENSION INFLUENCES PULMONARY VASCULAR RESISTANCE. B.E. Marshall, C. Marshall, M. Magno and P. Lilagan*. Anesthesiology, U of Penn, Philadelphia, PA 19104

Six adult anesthetized sheep were mechanically ventilated and instrumented to allow measurement of pulmonary vascular resistance while the common bronchial artery was cannulated and perfused with blood from a pump oxygenator circuit at controlled PO_2, PCO_2 and pH. The mean results when lungs were ventilated (FiO_2) with oxygen or air and the bronchial blood oxygen tension ($PbrO_2$) was varied in random order were:

FiO_2	$P_{br}O_2$	Q_t	PAP	PAOP	PVR
1.00	700	3.84	24.0	11.5	3.25
1.00	60	3.88	23.7	12.0	2.99
0.21	10	4.11	27.4	11.5	3.91
0.21	20	4.08	27.0	11.6	3.77
0.21	40	3.87	28.9	10.6	4.71
0.21	60	3.85	29.3	10.9	4.79
0.21	80	4.01	29.5	11.7	4.03
0.21	100	3.91	24.2	11.5	3.67

When FiO_2=1, the PVR was not influenced by $P_{br}O_2$, but when FiO_2=0.21, the PVR increased significantly as $P_{br}O_2$ was decreased, reaching a maximum at $P_{br}O_2$ of 40 and 60 mmHg and decreasing again as $P_{br}O_2$ was decreased further. It is concluded that systemic hypoxia influences pulmonary vascular tone through the bronchial circulation.
This work supported by NIH GM29628.

50.4

THE EFFECT OF ATELECTASIS ON PULMONARY VASCULAR COMPLIANCE. L.D. Nelin*, D.A. Rickaby, J.H. Linehan and C.A. Dawson. Med. Coll. of WI, Milwaukee, WI 53226; Zablocki VAMC, Milwaukee, WI 53295 and Marquette Univ., Milwaukee, WI 53233.

There is some question about the mechanical effects of atelectasis per se, independent of hypoxic vasoconstriction, on pulmonary microvascular hemodynamics. Since in the atelectatic lung the capillaries are no longer surrounded by air one might expect a change in vascular compliance. To evaluate this possibility absorption atelectasis (ATEL) was induced in dog left lower lung lobes. The isolated lobes were then perfused with normoxic blood at a constant flow rate and dynamic (Cdyn) and static (Cst) vascular compliance and the vascular pressure distribution were measured using vascular occlusion (J. Appl. Physiol. 61: 1802, 1986). The lobes were then inflated to a transpulmonary pressure of 3 torr (FRC) and the measurements repeated. The results are as follows,

	Cdyn	Cst	Pa-Pv	Pc-Pv
	(ml/torr)		(torr)	
ATEL	0.58±0.21	0.80±0.19	7.7±2.3	3.7±1.4
FRC	1.03±0.31*	1.21±0.38*	6.5±2.1	2.3±0.6*

mean + SD, * different from ATEL $p<0.01$

Cdyn and Cst always increased with lung inflation. In atelectasis a larger fraction of the total pressure drop across the lung occurred downstream from the midpoint of the vascular compliance. These results suggest that atelectasis per se alters microvascular hemodynamics.

Supported by Dept. of Veterans Affairs and NHLBI HL19298.

50.5

EFFECT OF [O_2] ON SMALL INTRAPULMONARY ARTERY RESPONSE TO NOREPINEPHRINE (NE) AND SEROTONIN (5HT) IN NEONATAL LAMBS. Julie A. Dunn, Quillen-Dishner College of Medicine, East TN State Univ. 37614 and Vichien Lorch*, Dept. of Pediatrics, Univ. of TN, Knoxville, TN 37996

Oxygen is a potent and selective vasodilator in the pulmonary vascular bed. We studied the effect of [O_2] on the response of 3rd (800-1200 um diameter) and 4th (150-300 um diameter) generation intrapulmonary arteries in vitro to NE and 5HT in lambs 7-10 days old. Vessel segments were mounted on a myograph and length-tension curves were performed by stretching in increments and stimulating with 125 mM KCl. Dose-response curves were generated at 95%, 15% and 5% [O_2] measured with an O_2 electrode. [O_2] had no effect on 3rd generation response to NE. The 4th generation arteries did not respond to NE regardless of [O_2]. There were no differences in the response of 3rd and 4th generation vessels to 5HT at 95% and 15% [O_2]. However, at 5% [O_2] a potentiated response to 5HT occured at 4th generation arteries. Oxygen below physiologic levels may sensitize the neonatal pulmonary vasculature arteries to 5HT. This sensitization may exacerbate a number of disease states.

50.6

ISCHEMIA-REPERFUSION INJURY DOES NOT ALTER CANINE PULMONARY ARTERIAL SMOOTH MUSCLE REACTIVITY. N. Jin, C.S. Packer, T.C. Lloyd, and R.A. Rhoades. Dept. of Physiology/Biophysics, Indiana University School of Medicine, Indianapolis, IN 46202.

Vascular changes have been reported with ischemia-reperfusion injury in brain, heart, and gut. The present study investigated the influence of ischemia-reperfusion injury on pulmonary arterial smooth muscle (PASM) reactivity. Ischemia-reperfusion injury was produced in dogs by occluding the main artery to lower left lobes for 24 or 48 hours and then reperfusing for 4 hours. Right lower lobes served as controls. Right and left lung wet weight : dry weight ratios were compared. Pulmonary arterial rings were hung in tissue baths. P_o (maximum response to 80 mM KCl), and tension development in response to 5 x 10^{-7} M norepinephrine (NE), or 10^{-3} M serotonin (5-HT) were measured. Rates of tension development (dP/dt) and relaxation half times ($t_{1/2}$) were also measured. The left lower lobe showed a significant 4.5% increase in wet weight ($p<0.001$). P_o of 579 ± 95 g/cm^2 for ischemic-reprfused vessels was not different from 493 ± 73 g/cm^2 for controls. Similarly, mean active tensions of 436 ± 53 g/cm^2 and 703 ± 77 g/cm^2 developed by control arteries in response to 5 x 10^{-7} M NE and 10^{-3} M 5HT, respectively were not different from mean active tensions of 490 ± 92 g/cm^2 and 819 ± 174 g/cm^2 developed by ischemic-reperfused arteries in response to NE and 5HT, respectively ($p>0.05$). dP/dt in response to KCl, NE, or 5HT, were also not different for the control and test vessels. Finally, control and ischemic-reperfused arterial muscle ACh-induced relaxation $t_{1/2}$ were not different. Results show that ischemia-reperfusion caused lung edema while having no apparent effect on PASM reactivity, force-generating ability, or relaxation rate.

50.7

INTERALVEOLAR CAPILLARY RECRUITMENT HETEROGENEITY. W.L. Hanson, K.R. Kirk*, C.J. Wong*, R.L. Capen, and W.W. Wagner, Jr. Depts. Physiol. and Anesthesia, Indiana Univ. Med. School., Indnpls, IN 46202 and Biol. Dept., Colo. Coll., Colo. Spgs., CO 80903.

It is well established that pulmonary capillaries recruit as transmural pressure is raised. There is little information, however, on the relationship between capillary pressure and recruitment in a single alveolus and on whether alveolar walls in the same hydrostatic zone follow the same pressure-recruitment curve. We studied these relationships via a transparent thoracic window implanted in anesthetized dogs and oriented so that the uppermost surface of the lung (high zone 2) could be observed by in vivo microscopy. Capillary pressure was altered by inflating a left atrial balloon. The left atrial pressure transducer was zeroed at the level of the window. This caused left atrial pressure to be -5 to -8 torr before the balloon was inflated. As the pressure approached zero, zone 3 was entered. Recruitment was determined by measuring the total length of capillaries that were perfused by red cells in single alveolar walls. Both between dogs and within dogs there was significant variation of capillary pressure-recruitment curves. In some cases, alveolar walls were completely recruited at all left atrial pressures (-7 to +25 torr). Other capillary nets had steep pressure-recruitment curves and became nearly fully recruited just as left atrial pressures exceeded zero. Another group of alveolar nets resisted being recruited and had curves that did not plateau until pressures were >20 torr. This surprising variety implies that an unexpected amount of perfusion heterogeneity may exist not only within the same hydrostatic zone but even within a single acinus. Supported by NIH HL-36033.

50.8

EFFECTS OF cGMP PROBES, INDOMETHACIN AND ENDOTHELIUM ON RAT PULMONARY ARTERY RESPONSES TO HYPOXIA. R. Mathew*, H.A. Omar*, P.D. Cherry*, M.H. Gewitz* and M.S. Wolin. New York Medical College, Valhalla, NY 10595.

Our laboratory has previously reported that decreased pulmonary artery (PA) levels of cGMP and H_2O_2 may mediate the endothelium-independent (-E) tonic hypoxic contraction (HC) observed in bovine PA and that rat PA show an -E transient HC. In this study we further characterized the mechanisms of O_2-elicited responses in isolated rat PA. Rat PA precontracted with 10nM phenylephrine also show a brief initial hypoxic relaxation (HR) on exposure to N_2 atmosphere prior to the HC, which is enhanced in endothelium-intact (+E) PA and not inhibited by indomethacin (10μg/ml). The inhibitor of soluble guanylate cyclase (GC) activation, LY83583 (10μM), inhibits both the initial HR and the HC. In rat PA-E, the inhibitor of cGMP selective phosphodiesterase activity, M&B22948 (10μM), decreases tone under O_2, but not under N_2, producing an apparent enhancement of the HC. The data suggest that the endothelium can modulate the rat PA response to hypoxia, but a decrease in GC activity in PA smooth muscle appears to mediate the HC. (Supported by HL31069 & BRSG-RR05398).

50.9

PULMONARY VASCULAR DEVELOPMENT IN NEWBORN LAMBS. STRUCTURE-FUNCTION CORRELATION. R.P. Michel, J.B. Gordon*, K. Chu*. Dept. Pathology and Pediatrics, McGill University, Montréal, Québec, Canada.

Previously, we found in isolated perfused lamb lungs that hypoxic vasoconstriction of the middle segment (defined by inflow-outflow occlusion) diminished with age after cyclo-oxygenase inhibition. We hypothesized that this could be due to a decrease in peripheral muscularization of small arteries or veins which lie in the middle segment. To verify this hypothesis, since there are insufficient data on this species in the literature, we studied the pulmonary vascular morphometry in lambs of 4 age groups: 6-12 h (n=5), 2-4 days (n=6), 14 days (n=5) and 30 days (n=5). For this, the arteries and veins of one lung were injected with pigmented gelatin and barium and fixed by airways instillation. Sections were taken for light microscopy to assess % medial muscle thickness (%MT) and peripheral muscularization for several size categories of arteries and veins from <50 μm to >1000 μm. We found that 1. The %MT of small arteries dropped by 2-4 days, whereas those >500 μm continued to decrease up to 30 days; 2. Peripheral muscularization of small arteries fell with increasing age; 3. Veins changed less with age and had a lower %MT than arteries. These data therefore suggest that the degree of small arterial muscularization is a determinant of the vigor of hypoxic vasoconstriction. Supported by the MRC of Canada and the Québec Heart Foundation.

50.10

DEVELOPMENTAL CHANGES IN SENSITIVITY TO HYPOXIA-INDUCED PULMONARY VASOCONSTRICTION. JB Gordon*, S. Clément*, K. Chu* (Spon: RP Michel). Montreal Children's Hospital, McGill University, Montreal, Quebec, H3H 1P3.

Hypoxic pulmonary vasoconstriction (HPV) increases with age in isolated lamb lungs. This is in part due to greater modulation of HPV in younger animals. Another possibility is that the stimulus required to induce HPV is lower in younger animals. We determined the pressure-flow responses to FiO_2= .28,.1, .06 and .04 in isolated lungs of<1 day and 1 month old lambs. Results shown are change in pressure in response to hypoxia at flow 90ml/kg• min (mmHg ± SE) (*p≤.05 ANOVA and LSD).

Pressure at FiO_2 =	0.1		0.6		0.4	
<1 day (n 7)	1.3	0.8	1.0	0.8	13.4	4.6
1 month (n 9)	4.9	1.4*	8.0	1.7*	8.8	1.0

These results show that in lungs of<1 day old lambs there is little HPV at FiO_2= .1 or .06; while in 1 month olds HPV was substantial. At FiO_2=.04 there was no difference between ages However, HPV was variable in<1 day lungs (vigorous in 3, low in 4). The failure of<1 day old lungs to respond at FiO_2= .1 and .06 even when a strong response occurred at FiO_2= .04 suggests a developmental shift in the sensitivity of the sensor of hypoxia. This, like the greater modulation of HPV previously seen, might lead to the apparently lower HPV in lungs of younger lambs. Whether this occurs in intact animals remains to be determined. (supported by QHF).

50.11

EFFECT OF BLOOD FLOW RATE HISTORY ON VENULAR PRESSURES IN LUNGS OF NEWBORN RABBITS. CD Fike, & MR Kaplowitz. Dept. of Pediatrics, Baylor College of Medicine, Houston, TX.

To determine the effect of blood flow rate history on the pressure drop across venules, we isolated and perfused the lungs of 8 newborn rabbits. We continuously monitored pulmonary arterial (Ppa) and left atrial (Pla) pressures. Using the direct micropuncture technique we measured 20-60 um venular (Pven) pressures at successive blood flow rates (BFR) of 50, 200, and 50 ml·kg·min^{-1}. During micropuncture we adjusted Pla to 9 cm H_2O and kept airway pressure at 5 cm H_2O (zone 3). Table summarizes data, (BFR, pressures (cm H_2O) mean±SD, *different from value immediately preceeding):

BFR	Ppa	Pven	Pla	Pven-Pla	Ppa-Pla
50	18.0±2.0	10.5±1.1	9.1±.8	1.6±.9	8.7±1.9
200	26.0±2.6*	14.3±2.5*	9.5±.8	4.8±2.5*	16.3±2.3*
50	17.0±1.0*	10.7±1.1*	9.3±.7	1.4±1.0*	7.5±1.4*

We found that when BFR quadrupled: Ppa and Pven increased such that the pressure drop downstream of 60 um venules (Pven-Pla=Pd) tripled whereas the total pressure drop across the pulmonary circulation (Ppa-Pla=Ptotal) doubled. When, BFR was returned to baseline: Ppa, Pven, Pd, and Ptotal returned to baseline. Thus, the percentage of the total pressure drop across venules (Pd/Ptotal) increased from 21± 16 to 30±16% when BFR quadrupled and returned to 21±18% when BFR was returned to baseline. We conclude that in newborn lungs, venules >60 um diameter are poorly distensible and do not demonstrate pressure-flow hysteresis.

50.12

OBSTRUCTIVE PULMONARY VASCULOPATHY: MORPHOLOGY AND IN VITRO ARTERIAL RESPONSES TO 5-HT AND HISTAMINE. D. Lachance*, S. Kunicki*, E.A. Zorychta*, T.S. Hakim, R.P. Michel. Dept. Pathology and Physiology, McGill Univ., Montréal, Canada.

Previously, we reported that chronic unilateral pulmonary artery ligation in dogs increased vascular resistance in ligated left lower lobes (LLL) by 100% compared with contralateral RLL, primarily of the arteries, and demonstrated a hypersensitivity of these to 5-HT (FASEB J 3:A380, 1989). To study their morphology, we injected with pigmented gelatin and barium the vessels of LLL and RLL of 5 dogs after ligation of the left main pulmonary artery for 120 days. By light microscopy, % muscle thickness and peripheral muscularization of vessels were assessed. We also suspended ring sections of arteries from ligated and control lobes in an organ bath and generated cumulative dose-response curves for 5-HT and histamine from which PD_2 values were calculated. Morphology showed in ligated lobes numerous periarterial and perivenous bronchial collaterals, an increased % muscle thickness and peripheral muscularization of arteries, which explain largely their elevated resistance. No plexiform lesions were seen and venous changes were mild. In vitro responses showed that arteries from 3 of 4 ligated lobes had higher PD_2 values for 5-HT than contralateral ones (mean 6.38 versus 5.76), but not for histamine. This may explain the in vivo hyperreactivity, although no correlation was seen with degree of muscle thickening. Supported by the MRC of Canada.

50.13

WOOD SMOKE INHALATION INCREASES PULMONARY VENOUS RESISTANCE AND LUNG WATER. T.S. Hakim, G.F. Nieman, W.R. Clark*, and C.E. Bredenberg. SUNY Health Sci. Ctr., Dept. of Surgery, Syracuse, N.Y. 13210.

The effects of wood smoke inhalation (SI) on pulmonary vascular resistance (PVR) is not well known. In this study we tested the effects of SI on PVR in the isolated left lower lobe (LLL) of canine lungs. In addition the site of increase in vascular resistance was identified using the arterial and venous occlusion technique (AVO). The LLL was perfused in situ with autologous blood at a constant flow (505±33 ml/min). The total (ΔPt), arterial (ΔPa), venous (ΔPv), and middle (ΔPm) pressure gradients (mmHg) were measured by AVO. Following baseline measurement the LLL was ventilated with wood smoke (plywood and kerosene) for 2.5 min. Pressure measurements were repeated at different points for 1 hr after smoke. Samples of lung were taken for W/D ratio at the end of the experiment. Results are shown in the following table (X±SE, * = p<0.05 vs Baseline).

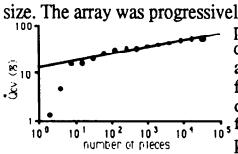
	Δ Pt	Δ Pa	Δ Pm	Δ Pv
Baseline	11.4±0.3	3.6±0.3	2.4±0.9	5.4±0.6
5 min Post Smoke	30.5±4.3*	4.6±0.3	5.2±1.0*	20.7±3.4*
(1 hr post smoke)	15.9±1.6*	4.1±1.4	4.4±0.7	7.8±1.2*

Smoke caused a significant increase in ΔPt due to a large rise in ΔPv. The increase in ΔPv was transient, it peaked at approximately 5 min, and returned toward baseline within 1 hr post smoke. In spite of this change in pressure lung water was increased (p<0.05) following smoke (W/D=6.6±0.3) compared to the normal left upper lobe (W/D=5.1±0.3). Therefore, SI in this isolated lung model causes pulmonary venoconstriction and pulmonary edema. Edema presumably occurs due to increasing vascular permeability and/or alveolar surface tension (Surgery 104:481-87,1989). High venous resistance could further accelerate the rate of edema formation.

50.14

HETEROGENEITY OF PULMONARY BLOOD FLOW: A FRACTAL APPROACH. Robb Glenny and H. Thomas Robertson. Department of Medicine, University of Washington, Seattle WA 98195

The heterogeneity of pulmonary blood flow as measured by the coefficient of variation of flow distribution (Q_{cv}) is dependent on the scale of measurement. However, fractal analysis is able to characterize Q_{cv} independently of scale. ^{99m}Tc labeled macroaggregate was rapidly injected intravenously at FRC (apnea) in 4 anesthetized supine dogs. The lungs were fixed in situ via vascular perfusion, preserving volume and orientation. The lungs were removed, air dried, embedded in polyurethane foam and sliced in 11.5 mm transverse sections. The sections were imaged on a planar gamma camera (FWHM= 4.1 mm) where pixel counts were then proportional to the local macroaggregate determined flow. A 3 dimensional array of blood flow measurements (voxel = 1.4 x 1.4 x 11.5 mm) was reconstructed and analyzed on a computer. Fractal analysis of flow distribution was used to examine Q_{cv} as a function of sampling size. The array was progressively subdivided and Q_{cv} calculated until each sample was a single voxel. Q_{cv} was fractal and could be characterized independently of scale by a fractal dimension (D) of 1.09 ± 0.02, obtained from the slope of the log-log plot (figure). A D of 1.0 reflects homogeneous flow and 1.5 reflects a random flow distribution. The fractal plot of Q_{cv} did not plateau, suggesting that the unit of perfusion in the lung is smaller than a voxel, 23.8 mm^3. The fractal dimension can be related to the coefficient of correlation (r) by the equation r = $2^{(3-2D)}$-1 (van Beek et al). The magnitude of flow to contiguous pieces of lung, regardless of size, is therefore correlated with r = 0.76. Fractal analysis is a new powerful method for describing the distribution of pulmonary blood flow.



50.15

IMMUNOREACTIVE ENDOTHELIN IS RELEASED BY THE ISOLATED RABBIT LUNG. A. Châtillon*, P. Cernacek*, Ch. Roussos, D.J.Stewart*. Department of Medicine, Royal Victoria Hospital, Montreal, Canada, MRC.

The mechanisms of regulation of endothelin (ET) production by in situ endothelium are unknown. The aim of the present investigation was to develop a model to study the production of ET by the isolated lung. Seven isolated rabbit lungs were perfused at constant flow (10 cc/minute) with modified Krebs solution and maintained inflated with a continuous positive pressure of 5 cm water using a normoxic gas mixture with 5% carbon dioxide. ET concentration in the venous effluent was measured using a radioimmunoassay (rabbit anti-ET-1 antiserum). In four experiments with non-recirculating perfusion, the rate of production of immunoreactive (ir)ET was 8.3 ± 1.8 pg/minute after an initial equilibration period of fifteen minutes, and remained constant up to one hour. In three additional experiments using recirculating perfusion, the initial concentration of irET in the effluent was 0.74 ± 0.82 pg/ml and, after one hour, reached a plateau of 2.05 ± 1.30 pg/ml, remaining constant over the next three hours, suggesting a balance between production and clearance of ET in this system. Therefore, these results demonstrate irET in the venous effluent from isolated perfused rabbit lungs. This model may prove to be useful in further defining the mechanisms regulating ET release from pulmonary endothelium in situ.

50.16

DIFFERENTIAL CONTRACTILE EFFECTS OF ENDOTHELIN UPON LUMINAL VERSUS ABLUMINAL EXPOSURE IN CALF PULMONARY VEINS. SYLVIA F. GUGINO* AND JAMES A. RUSSELL. SUNY AT BUFFALO, BUFFALO, NY 14214.

This study compared the contractile effects of endothelin added selectively to the luminal or abluminal surfaces of calf pulmonary veins mounted in Ussing chambers that were modified for the recording of isometric force generation. Endothelin concentration response curves (10^{-10} - 10^{-7}M) for luminal exposures were shifted significantly to the left compared to abluminal exposures. EC_{50}'s for luminal versus abluminal exposure were 2 x 10^{-9}M and 7 x 10^{-9}M endothelin, respectively. Moreover, addition of endothelin to the luminal surface of pulmonary veins precontracted by an abluminal exposure to endothelin caused an additional abrupt increase in tone that peaked and then decayed at a moderately rapid rate. This response was not observed when the order of exposure to endothelin was reversed. Neither removal of the endothelium nor pretreatment with 10^{-5}M indomethacin appeared to alter this difference in the contractile response to luminal versus abluminal exposure to endothelin. We conclude that luminal exposure to endothelin induces the release of a secondary mediator of contraction from non-endothelial cells in calf pulmonary vein. (Supported in part by NIH Grant HL34323).

50.17

FLOW THROUGH ZONE I LUNGS UTILIZES ALVEOLAR CORNER VESSELS. WJE Lamm*, RK Albert, TN Harwood*, KR Kirk*, WL Hanson, and WW Wagner, Jr. VAMC and U. of Wash., Seattle, WA 98122 and Ind. U., Indnpls, IN 46202.

We have observed that up to 15% of resting cardiac output can flow through lungs that are completely in Zone I. To determine whether the Zone I pathway utilizes alveolar corner or septal vessels we made microscopic observations of the alveolar capillaries in 5 anesthetized dogs. By implanting a transparent window in the ninth left intercostal space, and placing the animals in the right lateral decubitus position, video recordings could be made of the uppermost surface of the lung. From these recordings alveolar septal and corner vessels were classified depending on whether they were located within, or between alveoli. Recordings were made with various levels of positive end-expiratory pressure (PEEP) applied only to the left lung via a double lumen endotracheal tube. Flow through septal vessels stopped when PEEP was 5-10 cmH_2O > Ppa. However, both radiolabeled microspheres and in-vivo microscopy showed that flow continued until PEEP was 8-16 cmH_2O > Ppa and microscopy demonstrated that this flow occurred through alveolar corner vessels. The data support that alveolar corner vessels provide the pathway for blood flow under Zone I conditions.

50.18

REDUCED RED BLOOD CELL DEFORMABILITY AUGMENTS THE PULMONARY HEMODYNAMIC RESPONSE TO HYPOXIA. Michael P. Doyle and Benjimen R. Walker. Department of Physiology, School of Medicine, University of New Mexico, Albuquerque, NM 87131.

We investigated the effect of reduced red blood cell (RBC) deformability on pulmonary hemodynamics during acute hypoxic exposure and angiotensin II (AII) administration in isolated, perfused rat lungs. RBC suspensions were prepared using cells previously incubated in isotonic phosphate-buffered saline with or without 0.0125% glutaraldehyde. The washed RBCs were resuspended in isotonic bicarbonate buffered saline (with 4% albumin) to hematocrits of approximately 35%. The lungs were perfused with control and experimental cell suspensions in succession while pulmonary artery pressure (Ppa) was measured during normoxic (21% O_2) and hypoxic (3% O_2) ventilation. The pressor response to a bolus of AII was noted prior to each hypoxic exposure. Upon the attainment of a peak hypoxic pressor response, flow rate was changed so that pressure/flow (P/Q) curves could be constructed for each suspension. RBC deformability was quantified by a filtration technique using 4.7 μm pore polycarbonate filters. Glutaraldehyde treatment produced a 6% decrease in RBC deformability ($P<0.05$). Over the range of flow rates, Ppa was increased by 15-17% ($P<0.05$) and 26-31% ($P<0.05$) during normoxic and hypoxic ventilation, respectively, when stiffened cells were suspended in the perfusate. The responses to AII, when calculated as percent of control, did not differ between suspensions. We conclude that the presence of stiffened RBCs enhances the hemodynamic response to hypoxia but not to AII. This work was supported by HL42778 and a grant from the Cystic Fibrosis Foundation.

50.19

ISOLATED SMALL PULMONARY VEIN RESPONSE TO PROSTAGLANDIN F2a: EFFECT OF HYPOXIA AND CYCLOOXYGENASE INHIBITION. Karen J. Wendelberger & Jane A. Madden*, The Medical College of Wisconsin & VA Medical Center, Milwaukee, WI 53295.

Previously we studied the interaction of prostaglandin F2alpha (PGF2α) and hypoxia in isolated small pulmonary arteries. These interactions, however, have not been studied in isolated small pulmonary veins. Ring segments 2 mm long were cut from small pulmonary veins (200 - 400 μm diameter, threaded with two 22 μm tungsten wires. The wires were fastened over the jaws of open stainless steel rings. One ring was anchored and the other attached to a sensitive load cell (Kulite Semiconductor, Ridgefield, NJ). The veins were suffused with physiologic saline solution aerated with a gas mixture giving a PO_2 of 140 torr, PCO_2 of 35 torr, pH of 7.35 and temperature of 37 °C. The resting diameter was measured and the vessel stretched to 2.5 x its initial diameter. After 1 hour of equilibration the vessels were constricted with norepinephrine (10^{-6} M) and endothelial function determined by relaxtion to acetylcholine (10^{-6}M). Cumulative dose response curves to PGF2α were performed under normoxic and hypoxic conditions in the presence and absence of ibuprofen (10^{-5}M). As in arteries, neither hypoxia nor ibuprofen changed the efficacy of the PGF2α response. In contrast to the lack of effect seen in arteries, hypoxia decreased the potency of PGF2α in veins. Ibuprofen partially reversed this decrease, suggesting the release of additional vasodilating substances by hypoxia. While ibuprofen increased the potency of PGF2α in normoxic arteries, it had no effect on the potency of the response in veins under these conditions. These findings demonstrate significant differences in the response of arteries in veins to PGF2α and hypoxia.

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50.20

PULMONARY VASCULAR IMAGING USING CINE MR: A NON-INVASIVE APPROACH TO DYNAMIC IMAGING OF THE PULMONARY CIRCULATION. W.B. Gefter*, H.I. Palevsky, H. Hatabu*, B.J. Dinsmore*, N. Reichek*, L. Axel*, H.Y. Kressel*. Univ. of PA., Philadelphia, PA. 19104

Cine gradient-recalled (GRASS) MR, having sensitivity to flow and high temporal resolution, may yield both morphologic and dynamic flow-related information in the pulmonary vasculature. Using this technique we evaluated pulmonary vessels in 12 normal subjects and 8 patients with pulmonary hypertension. Normal pulmonary arteries and veins, imaged to at least subsegmental branches in 92%, were characterized by distinctive signal intensity and diameter variations as well as motion of the vessels occurring during different phases of the cardiac cycle. Patients with pulmonary arterial hypertension (N=8), in addition to showing morphologic vascular changes (wall thickening, vessel dilatation), demonstrated abnormally rapid acceleration and deceleration of velocity-related signal in the main pulmonary artery (PA) and loss of the normal pulsatile systolic increase and diastolic decline in intensity and diameter of the proximal PA's. These findings suggest reduced pulmonary arterial compliance and increased impedance in pulmonary hypertension. These preliminary results indicate that cine MR holds promise in studying patients with pulmonary vascular disease and in investigating pathophysiology in the pulmonary circulation.

50.21

EFFECTS OF ACIDOSIS AND ALKALOSIS ON HYPOXIC PULMONARY VASOCONSTRICTION (HPV) IN DOGS. S. Brimioulle*, P. Lejeune*, J.L. Vachiery*, M. Leeman*, C. Mélot*, R. Naeije. Laboratory of Cardiorespiratory Physiology, Erasme University Hospital, Brussels, Belgium.

Effects of acidosis and alkalosis on HPV were studied in 32 dogs, anesthetized and ventilated (RR 12/min, VT 30 ml/kg) in hyperoxia (FiO2 0.40) and in hypoxia (FiO2 0.10). Cardiac output was kept constant (3 L/min.m2) by inflation of a balloon in the inferior vena cava, to prevent passive changes in pulmonary arterial pressure. Arterial pH was decreased from 7.40 to 7.20 or increased from 7.40 to 7.60 by steps of 0.05 U. Isocapnic metabolic acidosis was induced with HCl 2 mmol/kg.hr, and metabolic alkalosis with Carbicarb (isomolar NaHCO3 and Na2CO3) 5 mmol/kg.hr. Constant ventilation PaCO2 changes were obtained by modifying FiCO2. HPV, defined as the hypoxia-induced increase in pulmonary arterial - capillary wedge pressures gradient, changed linearly with pH from

5 ± 2 to 9 ± 2 mmHg in metabolic acidosis (n = 8) (*)
6 ± 2 to 1 ± 1 mmHg in metabolic alkalosis (n = 8) (*)
6 ± 1 to 6 ± 1 mmHg in respiratory acidosis (n = 8)
5 ± 2 to 2 ± 1 mmHg in respiratory alkalosis (n = 8) (*)

(mean ± SEM, * : $p < .001$ by trend analysis)

Metabolic acidosis and alkalosis thus respectively increase and decrease HPV. The fact that respiratory acidosis did not affect HPV suggests a direct vasodilating effect of CO2 on the pulmonary vessels.

51.1

OLEIC ACID INJURY CAUSES INCREASED ^{22}Na MOVEMENT FROM AIRSPACES OF ISOLATED PERFUSED RABBIT LUNGS.

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We examined the movement of Evan's blue labeled albumin (EBA) and radioactive sodium (^{22}Na) among the airspace, perfusate and bath compartments of isolated rabbit lungs. In the control group (C) lungs were obtained from healthy rabbits with no prior intervention while in the injury group (OA) rabbits received 0.03 ml/kg of oleic acid intravenously and were then ventilated for 90 min before lung removal. The airspaces of 10 lungs were filled with a buffered solution containing EBA and ^{22}Na. The perfusate and the solution in which the lungs were immersed (bath) consisted of the same buffered 3 gm/dl albumin solution. Both groups were perfused for two hours at a pulmonary artery pressure of 12 mmHg and a left atrial pressure of 2 mmHg. Samples of each compartment were obtained at intervals to 120 min after the start of perfusion. Airspace fluid volume was determined by mass balance in an iterative fashion. The table shows the percentage of initial amounts of EBA and ^{22}Na that were in each compartment at the end of two hours of perfusion.

	22Na(C)	22NA(OA)	EBA(C)	EBA(OA)
Airspace	47.8±12.3*	22.0±2.2	88.8±6.9	74.2±12.7
Bath	5.3±1.3*	43.8±24.9	11.0±6.4	24.0±13.6
Perfusate	20.5±15.0	27.8±25.0	0.3±0.5	1.8± 1.5

* indicates $p<0.05$ when compared to oleic acid

We conclude that sodium moves out of the airspaces of oleic acid injured lungs faster than non-injured lungs through pleural space and/or lymphatics. To the extent that this enhanced transport is active, it may be increased therapeutically. (Supported by HL30835 and HL07605)

51.2

DIFFERENTIATION OF Na^+ TRANSPORT PATHWAYS BY AMILORIDE DOSE-RESPONSE RELATIONSHIP IN ISOLATED RAT LUNGS.

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We investigated the dose-response relationship for amiloride-sensitive Na^+ transport in the isolated perfused rat lung. Airspaces of degassed rat lungs were instilled with KRB solution containing ^{22}Na, ^{14}C-sucrose and FITC-Dextran (20,000 M.W.). Amiloride (10^{-6} M to 2×10^{-3} M) was added to the KRB perfusate at 32 min. Samples of the single-pass perfusate were taken at 5 min intervals following the instillation to analyze for tracer appearance in the vascular space. Based on Fick's First Law of Diffusion, tracer PS values were calculated. The effects of the amiloride dose on the PS product for Na^+ were analyzed with a dose-response relationship. The curve exhibited a typical dose-dependent inhibition of Na^+ transport by amiloride in the range of 10^{-6} M to 10^{-3} M. Amiloride showed a maximal % change in PS of 47% at 2×10^{-3} M, an ED_{50} of 5.45×10^{-5} M, and a log dose-response slope of 3.678 between the 15% and 85% maximal effects. The correlation coefficient for the curve fit was 0.81. An amiloride dose of 3×10^{-3} M appeared to be toxic to the lungs. Literature values assume that amiloride at doses of $\leq 10^{-6}$ M inhibit Na^+ conductance channels and amiloride at doses of $> 10^{-6}$ M inhibit the Na^+/H^+ exchange pathway. Based on these values, it appears that up to 30% of the Na^+ transport inhibited by amiloride in the isolated rat lung passes through the Na^+ channels. Thus, the presence of Na^+ channels in the intact alveolar epithelium is important for the clearance of Na^+ from distal airspaces of the normal lung.(Supp: NIH HL38310).

51.3

ANTIPROTEASE, ULINASTATIN, PREVENTS ALLOXAN-INDUCED LUNG INJURY IN ANESTHETIZED DOGS.

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We have demonstrated that alloxan-induced lung injury is prevented by oxygen radical scavengers. We studied to what extent this injury is prevented by urinary multiheaded antiprotease (Ulinastatin). We designed three protocols in anesthetized dogs; 1) Saline (20ml/kg/h) (Control, n=5), 2) Alloxan (75mg/kg) + Saline (Alloxan,n=5), 3) Ulinastatin (50,000 u/kg) + Alloxan + Saline(Ulinastatin,n=5). We followed all the dogs for 3 h. Alloxan caused the following significant changes; decrease in white blood cell and platelet counts for 3 h, increase in Tx B2 and 6-keto-PGF1a, increase in extravascular lung water (Qwl/dQl, 8.8+3.6g/g, mean+SD). Ulinastatin significantly suppressed most of the alloxan-induced effects; unchanged white blood cell counts, Tx B2, 6-keto-PGF1a and Qwl/dQl (4.6+2.0g/g). Electron microscopically, Ulinastatin prevented swelling of pulmonary endothelium. We conclude that alloxan-induced lung injury is in part prevented by Ulinastatin through antiproteolytic mechanism and antioxidant action.

51.4

ENDOTOXIN PROTECTION OF MICE FROM HYPEROXIA.

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Research on endotoxin protection from oxygen toxicity is presently limited to the rat model since only rats have been protected by endotoxin. This study reports that endotoxin also extends survival of adult male mice in hyperoxia (> 99% oxygen at 1 ATA). Initially, male mice (30-45 g, Charles River-Kingston, Stone Ridge, N.Y.) were treated with either Boivin- or Westphal-extracted E coli endotoxin (Difco, 055:B5) and placed in hyperoxia. Mice receiving Boivin-extracted endotoxin (20 µg/mouse, i.p.) showed moderate protection (13/20 mice survived 120 hour exposure to hyperoxia) while mice receiving Westphal-extracted endotoxin (20 or 60 µg per mouse, i.p.) exhibited minimal protection (2/10 survived the exposure period). This contrasts with untreated male mice (1/10 survived exposure to hyperoxia) or retired female breeder mice receiving 20 µg Boivin-extracted endotoxin (1/18 survived exposure). This study demonstrates that age, sex, or the extraction method used to obtain endotoxin, and possibly the time of year when endotoxin is administered, are important variables in allowing endotoxin protection of mice against oxygen toxicity.

(CF-1 mice were used in this study.)

51.5

SINGLE LUNG AUTOTRANSPLANTATION INDUCES GLUTATHIONE AND GLUTATHIONE PEROXIDASE ACTIVITY FOLLOWING REIMPLANTATION.

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The pulmonary reimplantation response (PRR) is a form of membrane permeability pulmonary edema occurring after lung transplantation. This response may be due to activation of oxygen-derived free radicals. Glutathione (GSH) could decrease free radical formation by elimination of hydrogen peroxide and organic hydroperoxides via the glutathione oxidation-reduction cycle. We hypothesized that lung autotransplantation could change glutathione metabolism and might increase free radical scavenging during the PRR. In order to test this hypothesis, six dogs underwent left lung reimplantation after the lung was flushed with Euro-Collins solution (EC) and submerged for three hours at 4°C. Five unmanipulated control dogs underwent bilateral pneumonectomies under operative conditions identical to autotransplanted dogs. Lung GSH concentrations and glutathione peroxidase (GSH-Px) activity were measured in all animal lungs after 1 hr of reperfusion.

	Controlα		Transplantedα	
	right	left	right	left
GSHβ	.005±.008	.005±.002	.019±.006δ	.011±.001δ
GSH-Pxγ	411±57	481± 55	919±118Ω	722± 91Ω

α Mean ± SE, β nM/mg DNA, γ uM 1Cl-2,4 Dinitrobenzene oxidized/min/mg DNA, δ Different from controls at $p<.01$
Ω Different from controls at $p<.02$

GSH concentrations and GSH-Px activities were induced in both the native and the autotransplanted lungs compared to controls. Despite this augmentation of components of glutathione redox cycle components, the autotransplanted lungs were noted to develop the PRR as assessed by CXR evidence of pulmonary edema and increases in lung water.

51.6

THE EFFECT OF XANTHINE OXIDASE INHIBITION OR DEPLETION ON ISCHEMIA-REPERFUSION INJURY IN ISOLATED RABBIT LUNGS.

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The role of xanthine oxidase in ischemia-reperfusion injury was studied in isolated rabbit lungs by either inhibition with allopurinol or depletion via Tungsten-enriched/Molybdenum deficient diet. New Zealand white rabbits were anesthetized (sodium pentobarbital 30 mg/kg I.V.) and the heart-lung block was removed and constant flow perfused with whole blood at 37°C. Endothelial permeability was assessed using the capillary filtration coefficient ($K_{f,c}$). Total vascular resistance (R_T) was also calculated. Lungs underwent 4 protocols: (1) control (n=4), (2) ischemia-reperfusion (n=5), (3) ischemia-reperfusion + allopurinol (100 μM)(n=5), (4) ischemia-reperfusion + Tungsten diet (n=6). Endothelial permeability ($K_{f,c}$, ml/min/cmH_2O/100g) was increased after 2 hours of ischemia-1 hour reperfusion (0.097±0.039 baseline to 0.171±0.018). This increase was inhibited by allopurinol (0.120±0.032 baseline to 0.106±0.011) and by the Tungsten-enriched diet (0.211±0.084 baseline to 0.182±0.084). R_T tended to increase after I-R and this increase was attenuated by the allopurinol addition and the Tungsten-enriched diet. These data demonstrate that endothelial permeability increases after ischemia and reperfusion and that this change can be blocked by xanthine oxidase inhibition or depletion. (Supported by NIH HL22549.)

51.7

EFFECTS OF α_1-PROTEASE INHIBITOR ON BLEOMYCIN-INDUCED PULMONARY FIBROSIS. Kazutetsu Aoshiba*, Atsushi Nagai and Takao Takizawa. Tokyo Women's Medical College Shinjuku, Tokyo, 162

To clarify the role of α_1-protease inhibitor(α_1-Pi) in the pathogenesis of pulmonary fibrosis, we studied the effect of the administration of α_1-Pi on bleomycin-induced pulmonary fibrosis in hamsters. Male Golden Syrian hamsters(5-weeks old), given 1mg/100g body wt of bleomycin instratracheally, were classified into the two groups:the experimental group(B-Pi)-7 animals given intraperitoneally human α_1-Pi(6-18mg) dissolved in saline once a week for 4 weeks, the control group(B-C)-6 animals given intraperitoneally the same volume of saline at the same day as those of the experimental group. 30 days after the treatment with bleomycin, the animals were sacrificed under anesthesia with pentobarbital. After the bronhoalveolar lavage was done, their lungs were fixed by intratracheal instillation of 2.5% glutaraldehyde and cut for histological examination. The results were as follows:1) Specific lung volume(lung volume/body wt) were larger in B-Pi than in B-C ($p<0.05$). 2) On histological observation, the severity of pulmonary fibrosis was lesser in B-Pi than in B-C. 3) On morphometrical analysis, the volume fraction of alveolar wall and the mean alveolar thickness were smaller in B-Pi than in B-C-($p<0.05$). 4) The cell numbers of macrophage, neutrophil and lymphocyte were lesser in B-Pi than in B-C($p<0.05$). It is concluded that α_1-Pi reduced the severity of bleomycin-induced pulmonary fibrosis in hamsters.

51.8

The Function of Neutrophil and Alveolar Macrophage in Bleomycin-induced Alveolitis. Y.Ishihara,A.Nagai,A.Aoshiba, J.Kagawa, Tokyo Women's Medical College, Tokyo, Japan

Superoxide anion(O2-)production from alveolar macrophage(AM) and neutrophil(PMN)may be of crucial importance in inflammatory process of lung fibrosis. Relatively little is known about function and its regulation of AM and PMN in Bleomycin-induced alveolitis. AMs were recovered by alveolar lavage fluid and PMN from peripheral blood in control and Bleomycin(2U)treated guinea pig, and were separated by discontinuous Percoll gradient method.The resulting cells adhered contained 0.25x106cells in 96 microtiter well composed of >95%AM,PMN and >90%AM,>99% PMN viable by trypan blue dye exclusion.O2-production from cell monolayers was assessed by superoxide dismutase inhibitable ferricytochrome c reduction in the presence or absence of phorbol myristate acetate(PMA)at 10-8 to 10-6M.Also, morphology of lung and cells were studied by electron microscopy.

Spontaneous O2-production of PMN in the absence of PMA at day7 of Bleomycin treatment was significantly higher than that in control, but not in AM.However at day28 of Bleomycin treatment O2-production in AM and PMN showed as same as the amount of control group in the absence and presence of PMA.The pulmonary fibrosis was found in the lung at day28 of Bleomycin treatment.These results suggest that the function of PMN which is independently of protein kinase c activation,is activated in Bleomycin-induced acute lung injuly, but not in chronic injury. And PMN may play a more important role in Bleomycin alveolitis than AM.

51.9

METHYLPREDNISOLONE (MP) DOES NOT PREVENT INCREASED PULMONARY VASCULAR PERMEABILITY FOLLOWING WOOD SMOKE INHALATION. G.F. Nieman, T.S. Hakim, W.R. Clark*, and D. Goyette*. SUNY Health Sci. Ctr., Dept. of Surgery, Syracuse, N.Y. 13210.

Wood smoke inhalation (SI) in the dog lung model is associated with pulmonary inflammatory reaction, vascular injury and increased lung water (Surgery 105:481-487, 1989). Anti-inflammatory agents (steroids) are thought to have a protective action in various models of lung injury. In this study we tested the effect of Methylprednisolone (MP) in preventing the increase in pulmonary vascular permeability following SI. The left hilar afferent lymphatic was cannulated in anesthetized dogs and 30 mg/Kg of MP was given (i.v.) 2 hrs presmoke. Following baseline measurements of lymph (CL) and plasma (CP) total protein concentration and lymph flow (QL ul/min), smoke (plywood and kerosene) was delivered to the dogs via the ventilator for 5 min. Left atrial pressure was increased (Pla = 16.7±2.2) to obtain a filtration independent measurement of protein clearance. The steady state values of SI+MP (n=5) are compared to smoke without MP (SI, n=7) and normal lungs (Control, n=14) in the following table:

	Baseline		Increased Pla	
	QL	CL/CP	QL	CL/CP
SI	27±9	0.76±0.03	136±15*	0.67±0.02
SI+MP	13±3	0.68±0.06	90±32*	0.64±0.04
Control	48±10	0.69±0.02	112±20*	0.55±0.03

In all three groups there was a marked increase in QL subsequent to ↑ PLa. However, unlike the controls, the CL/CP ratio failed to "washdown" in the two smoke groups. We therefore conclude that smoke inhalation increased vascular permeability to proteins and that MP did not prevent this injury.

51.10

MORPHOLOGIC CHANGES IN SHEEP LUNG FOLLOWING INTRAVENOUS RECOMBINANT HUMAN TUMOR NECROSIS FACTOR ALPHA (rTNFa) MIMIC THOSE OF ENDOTOXEMIA. J. Johnson, M.D.; K.L. Brigham, M.D.; B. Meyrick, Ph.D. Departments of Pathology and Medicine, Center for Lung Research, Vanderbilt University Medical School, Nashville, TN

Tumor necrosis factor alpha (TNFa) has been implicated as an early and pivotal mediator of endotoxic shock. Its infusion into awake sheep causes changes in lung function similar to endotoxemia (Johnson et al., J. Appl Physiol 66:1448-54, 1989). Five anesthetized open-chest sheep with a jugular venous Swan-Ganz catheter and a carotid arterial line received 0.01 mg/kg rTNFa intravenously over 20 minutes. Lung biopsy tissue was obtained at baseline, 7.5, 15, 30, 60, 120, 180, and 240 min after the start of infusion. As in the awake animal, the physiologic response included early transient pulmonary hypertension (baseline = 17.4±1.6; 7.5 min = 25.4±4.2: mean±SEM) and prompt and persistent leukopenia. Light microscopy revealed progressive pulmonary congestion and granulocyte sequestration (4.8±1.6 x baseline granulocytes per 100 alveolar profiles at 1 hr; 5.7±1.8 x baseline at 3 hr) as well as thickened alveolar walls and, from 2 hr, mononuclear cell infiltration into the bronchovascular bundles. Electron microscopy confirmed granulocyte sequestration within the microvasculature and revealed increased numbers of pulmonary intravascular macrophages and lymphocytes. Other changes included progressive endothelial cell and type II pneumonocyte injury from 30 min, and development of interstitial edema between 1 and 4 hr. Early inflammatory cell sequestration in the pulmonary microvasculature may, as with endotoxin, contribute to the pathogenesis of TNFa-induced lung injury. Supported by HL 19153.

51.11

OCCLUSION OF THE BRONCHIAL ARTERY ATTENUATES PULMONARY EDEMA FORMATION AFTER INHALATION INJURY. S. Abdi*; L.D. Traber*; D.N. Herndon; D.L. Traber. Univ. of Texas Med. Br. & Shriners Burns Inst., Galveston, TX 77550

We have shown that there is a marked increase in bronchial blood (Q_{br}) and lung lymph flows (Q_l) after inhalation injury. The present study investigates the role of the bronchial microvasculature in the formation of pulmonary edema after cotton smoke inhalation. We measured hemodynamics and Q_l on 12 chronically instrumented sheep. Group I (n=7) had an occluder and an ultrasonic transit time flow probe mounted around the bronchial artery. Group II (n=5) had neither occluder nor probe. Each sheep was insufflated with cotton smoke (4x12 breaths at <40°C) using a modified bee smoker. The bronchial artery of Group I sheep was occluded throughout the experimental period. After the study the animals were sacrificed and samples of lung taken for measurements of wet to dry-weight ratio (W/D). We found that there was a significant increase in Q_l in both groups; however, this increase 24 hrs after injury was three times greater in Group II than in Group I. Bloodless W/D ratio of the Group I was less than Group II. No significant hemodynamic differences were found between the two groups. We conclude that an increase in Q_{br} after inhalation injury may be partly responsible for the formation of pulmonary edema and this can be attenuated by reducing the systemic blood supply to the airways. (Supported by HL37411, GM33324)

51.12

EFFECT OF HYALURONIDASE ON THE RESPONSE OF HILAR INTERSTITIAL PRESSURE TO WATER ACCUMULATION IN LIQUID-FILLED RABBIT LUNGS. Jingwen Li*, Qiu-Huo Yang*, Sundaresh Ganesan* and Stephen J. Lai-Fook. University of Kentucky, Lexington, KY 40506.

Hyaluronidase caused an increased hydraulic conductivity in the rabbit's pulmonary interstitium (Faseb J. 2:A1870, 1988). We used the micropuncture technique to measure interstitial pressure around a partially exposed vein near the hilum of the isolated rabbit lung. Control lungs (n = 5) were degassed and inflated with a 3% albumin solution to a transpulmonary pressure (Ptp) of 5 cmH_2O. Treated lungs (n = 4) were inflated with albumin solution containing hyaluronidase (0.02%). Interstitial pressure was measured continuously with time (t) until it equilibrated to the alveolar pressure (5 cmH_2O). The interstitial pressure (Pi) response was similar to the step response of a resistance (R) in series with a capacitor (C): $Pi = Ptp[1- \exp(-t/to)]$, where to = RC is the time constant for interstitial filling. The time constant for the control lungs averaged 2.5 h, which was significantly longer than the time constant of 1.2 h for the treated lungs. Assuming that interstitial compliance was constant, hydraulic resistance to fluid movement through the pulmonary interstitium was reduced two-fold as the perivascular fluid cuffs expanded in the presence of hyaluronidase. Hyaluronan is a major determinant of pulmonary interstitial conductivity. (Suppported by HL 40362).

51.13

INTERSTITIAL PULMONARY PRESSURE IN ANESTHETIZED, PARALYZED RABBITS WITH INTACT PLEURAL SPACE. Giuseppe Miserocchi and Daniela Negrini. Ist. Fisiologia Umana, Università di Milano.

Rabbits were anesthetized, paralyzed, oxygenated with humidified 50% O_2 in air via a tracheal tube and kept in either supine or lateral posture. A small area of an intercostal space was cleared of intercostal muscle down to the endothoracic fascia. The latter was then carefully stripped leaving only the parietal pleura through which pulmonary structures (alveoli, septa, vessels) could be clearly identified. Pulmonary interstitial pressure (Pip) was measured using a servonulling system connected to 2-3μ tip glass micropipettes that were inserted through the parietal pleura under stereomicroscopic view (x 150-200). Depth of recording averaged 263±122 (SD)μ from the parietal pleura. At 25 and 70% of lung height Pip was respectively: -9.4±1.1 (SD) and -12.4±2.4 cm H_2O. The data indicate that, with intact pleural space, Pip is about 7 cm H_2O more subatmospheric than pleural liquid pressure at comparable height.

51.14

HYDRAULIC CONDUCTIVITY DETERMINED BY THE SPLIT DROP TECHNIQUE IN PULMONARY VENULE OF RAT. Ren-Li Qiao* and J. Bhattacharya, St. Luke's-Rsvlt. Hosp. Ctr., Depts. Physiol. & Med., Columbia Univ., New York, N.Y. 10019.

We have previously reported split-drop hydraulic conductivity (Lp) for single microvessels of dog lung (JAP 64:2562,1988). Here we report split-drop data for rat lung. In 5 experiments, we excised rat lungs and held them at constant alveolar pressure of 5 cmH_2O. After a period of blood perfusion (12 ml/min), we stopped blood flow and held vascular pressure at either 5 or 10 cmH_2O. At each pressure we micropunctured a venule twice, first to inject an oil drop and then to split the oil drop with albumin solution (5.8 g%, pH=7.40). From measurements of venule diameter (20-40 μm) and of time dependent split-drop length (i.e. distance between oil menisci) we computed filtration rate at time=0 (Jv) as shown in the table (mean±SD).

Pressure (cmH_2O)	5	10
Jv (10^{-6} ml/(cm^2.s.))	-2.2±.6	2.4±3.6

At the higher pressure Jv was significantly higher ($P<.01$). Lp calculated as the ratio of the differences in Jv and pressure, averaged 5.4±2.6 $x10^{-7}$ ml/(cm^2.s.cmH_2O). We conclude that for rat and dog lungs, venular Lp are similar (Supported by HL 36024, HL 01696 and AHA 860681).

51.15

PERMEABILITY-SURFACE AREA PRODUCT (PS) REFLECTION COEFFICIENT (σ) AT MAXIMAL PROTEIN DIFFUSION IN PULMONARY CAPILLARIES. **M. Ishibashi, R.K. Reed, M.I. Townsley, J.C. Parker, A.E. Taylor, Dept. Physiology, Univ. South Alabama, Mobile, AL 36688.**

We determined σ and PS for total protein using a new analysis of lung lymph protein flux in anesthetized dogs. At the point where the relationship between lymph protein clearance and lymph flow (Jv) changes from a curvilinear to linear function, the Peclet number ($X=(1-\sigma)Jv/PS$) attains a unique value at the point of maximal diffusive transport (Reed et al., FASEB J. 3:A1399, 1989). From the values of σ, X, and Jv at this point (Jv,md), a flow-independent value can be obtained for PS, where $PS=(1-\sigma)Jv,md/Xmd$. Total protein flux data collected from 6 canine lung lymph experiments yielded (mean±SE): σ=0.665+0.024, PS=15.0+2.4μl/min; and Jv,md=29.6+5.1μl/min. Maximal protein diffusion occurred at a lymph flow rate of 3.2±1.0 times control and accounted 45% of the total protein flux at that point. Although at higher flow rates the contribution of convection to protein clearance increased, our PS values were determined at Jv,dm, so were independent of lymph flow rate. This method allowed both PS and σ to be determined at relatively low lymph flow rates (supported by NIH HL24571 and HL22549).

51.16

HOW ACCURATE IS THE TRICHLORACETIC ACID PRECIPITATION ASSAY FOR FREE RADIOIODINE? MA Matthay, RH Hastings*. Card Res Inst., Depts Anes & Med, Univ Calif, San Francisco, CA 94143.

Radioiodinated proteins contain some free radioiodine that needs to be measured accurately to determine the quantity of radiolabeled protein present in any biologic compartment. We investigated the trichloracetic acid (TCA) precipitation method of measuring free iodine for two potential errors: rebinding of iodine to protein and incomplete precipitation of protein. We counted a sample in a gamma counter, added 10% TCA, centrifuged the sample, and counted the supernatant. We added 125Iodine to 4 stock protein samples containing 125I-albumin. The TCA assay detected 84.0±5.9 cpm additional 125Iodine compared to the 84.8±11.6 added. We also did the TCA test with and without 5 mg/ml cold NaI to test for rebinding of iodine to protein. The free iodine measured in the 125I-albumin stock with and without cold NaI was 1.89±.08 & 1.85±.09%, respectively. Finally, the free iodine in 125I-albumin and 125IgG was measured by TCA assay and paper chromatography. The data are summarized in the table.

	% Free Iodine Detected	
	125I-albumin	125IgG
TCA	1.3 ± .2	27.3 ± 2.3
Chromatography	1.4 ± .2	26.9 ± 1.3

The coefficient of variation of the TCA assay was 5%. We conclude that the TCA method is accurate, reiodination of protein does not occur, and albumin and IgG are completely precipitated by TCA. [Supported by NIH (HL40626)].

51.17

DIFFERENTIAL CLEARANCE OF ALBUMIN AND IMMUNOGLOBULIN G FROM THE LUNGS OF ANESTHETIZED, VENTILATED RABBITS. RH Hastings*, MA Matthay. Cardiovasc Res Inst., Depts Anesthesia & Medicine, Univ Calif, San Francisco, CA 94143-0130

Differential clearance of different sized proteins from the air spaces and lungs has not been systematically studied. We reported very slow removal of albumin from the air spaces and lungs of dogs and sheep (JAP 65:585, 1988; JAP 59:928, 1985). We have now quantified the relative clearance of albumin and immunoglobulin G (IgG) from the lungs of 7 anesthetized rabbits. We instilled 2 ml/kg of autologous plasma labeled with human 131I-albumin and 125I-IgG into the air spaces of one lung. Then we sampled the blood every 30 min and removed the lungs after 4 h. Free 125I and 131I were measured by trichloracetic acid precipitation. The table summarizes the recovery of the instilled tracer proteins in the blood and the lung homogenate after 4 h (mean ± SD, *$p<.05$).

	Tracer Protein Recovered (% of instilled)	
	Blood	Lung Homogenate
131I-albumin	2.8 ± 2.8	92.6 ± 6.0
125IgG	1.0 ± 0.9*	96.4 ± 4.9*

Albumin (66,000 MW) was cleared from the lung significantly faster than IgG (135,000 MW), either because of faster clearance across the alveolar epithelium or more rapid diffusion into the blood from the lung interstitium. [Supported by NIH HL40626].

51.18

ALVEOLAR FLOODING OCCURS WITH INCREASED EXCHANGE OF PROTEINS BETWEEN THE AIR AND INTERSTITIAL SPACES OF THE LUNGS. B.T. Peterson, M.L. Collins*, and A.O. Azghani*. Univ. of Texas Health Center at Tyler, Tyler, Texas 75710

We measured the lung lymphatic concentration of aerosolized ^{99m}Tc-human serum albumin (^{99m}Tc-HSA) in anesthetized sheep to assess the importance of protein exchange across the lung epithelium in the pathogenesis of alveolar flooding. After ventilating the sheep for 6 min with an aerosol of ^{99m}Tc-HSA we monitored its concentration in the lymph for 2 hours. The steady-state value is reported as a percent of its concentration in the air spaces. We induced a 20 cmH_2O increase in left atrial pressure (P_{la}) for 4 hs in 7 sheep, 7 had oleic acid-induced lung injury, 3 received an aerosol of Pseudomonas elastase to increase epithelial permeability to albumin, and 3 received both increased P_{la} and elastase. The degree of alveolar flooding in lung biopsies (0-4) is shown:

Group	No. of Sheep	Lymphatic [^{99m}Tc-HSA]	Flooding Score
CONTROL	5	.03 ± 0.02	0.9 ± 0.6
Increased P_{la}	7	.05 ± 0.01	1.3 ± 0.8
Lung Injury (Oleic Acid)	7	.31 ± 0.07*	3.9 ± 0.1*
Aerosol of Ps. Elastase	3	.09 ± 0.09	1.0 (n=1)
Inc. P_{la} + Ps. Elastase	3	.32 ± 0.14*	3.4 ± 0.5*

Alveolar flooding occured only when the lymphatic concentration of the ^{99m}Tc-HSA was elevated (*$p<0.01$ versus control). Increased exchange of proteins between the lung interstitium and the air spaces may be required for alveolar flooding.

51.19

TRANSPORT OF ALBUMIN, TRANSFERRIN AND MANNITOL INTO THE EPITHELIAL LINING FLUID. N.-H. Feng* and R.M. Effros Harbor-UCLA Med. Ctr. Torrance, CA 90509 & Med. College of Wisconsin, Milwaukee, WI 53226.

Very little is known about the rates at which solutes equilibrate between plasma and the fluid which lines the distal surfaces of the lung (epithelial lining fluid, ELF). In the present study, intravenous and intramuscular injections of human albumin, ^{113m}In-transferrin and ^{3}H-mannitol were administered to 20 anesthetized rats to maintain constant plasma concentrations. After intervals of from 1 to 60 minutes, the experiments were terminated by instilling 5 ml of isotonic saline into the tracheas at pressures below 3 cm H_2O and then removing about half within a 30 second interval. Plasma (P) and bronchoalveolar lavage fluid (BAL) concentrations of human and rat albumin and rat transferrin were determined by rocket immunoelectrophoresis, and urea and radioisotope concentrations were measured in these fluids. Average plasma concentrations did not vary by more than 10% from mean values during most of these studies. BAL/P ratios of urea, rat albumin and transferrin averaged 0.028 ± 0.002, 0.014 ± 0.003 and 0.011 ± 0.003 (SEM), respectively. After 1 hour, BAL/P ratios of ^{3}H-mannitol increased to 77 ± 7% those of urea, whereas BAL/P of human albumin increased to 76 ±14% of rat albumin ratios and BAL/P of ^{113m}In-transferrin increased to 82 ± 18% of unlabeled transferrin ratios. Unexpectedly rapid equilibration of these solutes is attributable to the high surface to volume ratios of the ELF. The relative nonselectivity of epithelial transport to molecules of different size suggests vesicular transport. (Supported by NIH grant HL18606).

51.20

TERBUTALINE AND CYCLIC NUCLEOTIDE ANALOGS FAIL TO STIMULATE SODIUM TRANSPORT OUT OF THE AIRSPACES OF HAMSTER LUNGS. William F. Waltz, Barbara E. Goodman, and Evelyn H. Schlenker. Department of Physiology and Pharmacology, University of South Dakota, School of Medicine, Vermillion, SD 57069.

The stimulation of sodium (Na^+) transport out of the airspaces of the lungs from mature BIO 14.6 dystrophic and Golden Syrian hamsters was investigated. Terbutaline, dibutyryl cyclic AMP (dbcAMP), and isobutylmethylxanthine (IBMX) have been shown to increase the rate of sodium transport out of the airspaces of the lungs of other mammals. In previous studies, we showed that active transport of Na^+ out of the airspaces of hamster lungs could be inhibited by amiloride. Airspaces were instilled with KRB solution containing trace amounts of ^{22}Na, ^{14}C-sucrose, and FITC-Dextran (20,000 M.W.). Samples of the single-pass perfusate were taken periodically thereafter. The permeability-surface area products (PS) were calculated based on the appearance of tracers in the vascular space and Fick's First Law of Diffusion. PS values in the isolated lung preparation were compared before and after the addition of terbutaline, dbcAMP, or IBMX to the perfusate. No changes in Na^+ PS after exposure to any of the pharmacons were seen in either group of hamsters. The cyclic GMP analog dbcGMP also did not change Na^+ transport. The failure of these agents to enhance Na^+ transport suggests that such stimulation may not be important for hamster lung fluid balance. This system may provide a model for studying lung fluid balance where the stimulation of Na^+ transport does not play a central role.(Supported by NIH HL38310, Sigma Xi Grant-in-Aid).

51.21

LUNG LUMINAL LIQUID IS NOT REMOVED VIA THE PLEURAL SPACE IN HEALTHY NEWBORN LAMBS. James J. Cummings*, David P. Carlton*, Francis R. Poulain*, and Richard D. Bland. University of California, San Francisco, CA 94143

The pathways by which luminal liquid leaves the lungs after birth are ill-defined. Previous studies showed that lung lymphatics normally drain only a small fraction of liquid in potential airspaces (J Appl Physiol 53:992, 1982). It is likely that the pulmonary circulation receives a greater amount of residual liquid present in the lung lumen at birth (Am Rev Resp Dis 134:305, 1986). Another potential route for clearance of luminal liquid is the pleural space. To study the importance of this pathway, we percutaneously placed silicone rubber catheters under local anesthesia in both pleural spaces of 5 lambs (age 3 ± 1 days) and measured net production of pleural liquid before and after tracheal instillation of warm, isotonic saline, 6ml/kg body weight. The lambs received pancuronium and morphine and were mechanically ventilated for at least 2 h before and 6 h after saline delivery, as pleural liquid was aspirated every 2-3 min. There was no significant change in either the amount or the protein concentration of liquid collected from the pleural catheters over time, suggesting that little if any residual lung liquid drains via the pleural space in healthy newborn lambs. Supported by PHS Grants HL 40802 and HL 27356.

51.22

LUNG VASCULAR RESPONSE TO RAPID INTRAVENOUS SALINE INFUSION IS SIMILAR IN PRETERM FETAL AND MATURE NEWBORN LAMBS. David P. Carlton*, James J. Cummings*, Francis R. Poulain*, and Richard D. Bland. Cardiovasc. Res. Inst. and Dept. of Pediatrics, University of California, San Francisco, CA 94143

To estimate lung vascular filtration coefficient (Kf) in preterm fetal and mature newborn lambs, we measured pulmonary arterial and left atrial pressures, lung lymph flow, and protein osmotic pressures in lymph and plasma of chronically catheterized fetal (130 ± 3 days gestation, wgt 3.4 ± .6 kg, n=7) and newborn (14 ± 3 days old, wgt 7.0 ± .9 kg, n=7) lambs during a 2 h control period followed by 3-4 h of rapid intravenous saline infusion, 250-500 ml/h. Calculated net filtration pressure increased 3-4 Torr during saline infusion in both sets of studies, and lung lymph flow per kg body weight also increased to a similar extent in fetuses (.59 ± .27 ml/h) and newborns (.55 ± .25 ml/h). Based on these measurements, Kf averaged .17 ± .05 for fetuses and .21 ± .11 for newborns. In 7 other studies we injected radiolabelled albumin intravenously and measured its rate of uptake in lymph relative to its disappearance from plasma under baseline conditions: turnover time averaged 160± 38 min in fetuses and 161 ± 37 min in newborns. These results suggest that lung vascular protein permeability is similar in healthy preterm fetal and mature newborn lambs. Supported by PHS Grants HL25816, HL/HD24056, HL40802, and HL27356.

51.23

MEASUREMENT OF H^+ SECRETION IN FETAL OVINE LUNG LIQUID T.A. Davis, H. Kuck, A.M. Perks, T.H. Maren, and S. Cassin Department of Physiology and Pharmacology, College of Medicine, University of Florida, Gainesville, FL 32610

Fetal lung liquid (LL) is secreted by the developing lung *in utero* and is necessary for proper lung growth and amniotic fluid volume. Secretion of LL is believed to be due to active Cl^- transport from blood to alveolar space. Although the concentration of Cl^- is high (14.7 mEq/L) in LL, HCO_3^- levels are low (2.4 mEq/L) compared to plasma (Cl^-, 104 mEq/L; HCO_3^-, 2.5 mEq/L). The average pH of LL is 6.2 compared to 7.34 for plasma. It is unclear why LL pH is low and how these conditions are maintained during development *in utero*. This study tests the hypothesis that there is active transport of H^+ into the alveolar space. Chronically catheterized sheep fetuses with exteriorized tracheal cannulae were used to study the effects of replacing 30 ml of LL with 30 ml of isotonic phosphate solution (Na_2HPO_4: NaH_2PO_4 = 4:1; pH=7.4) on LL pH and HCO_3^- concentration. An impermeant tracer, ^{125}I-albumin, was also mixed with LL to estimate LL volume. Changes in the ratio of Na_2HPO_4: NaH_2PO_4 were calculated from measured values of LL phosphate and pH at the beginning of each experiment after fluid replacement, and at the end of each 4-hr experiment. An average H^+ secretion of 3.42 ± 0.91 SE μmoles H^+/min was measured in 8 experiments. Methazolamide (32 mg/kg) in LL depressed H^+ secretion. This rate of acid secretion could lower the pH of an unbuffered solution from 7.34 to about 6.0 and is probably responsible for the low pH and low HCO_3^- of poorly buffered LL.
(Supported in part by NIH #HL10834).

51.24

THE USE OF ^{14}C-DIAZEPAM TO INTERPRET CHANGES IN EXTRAVASCULAR LUNG WATER. C.A. Dawson, D.A. Rickaby, D.L. Roerig, and J.H. Linehan. Med. Coll. of Wis., Milwaukee, WI 53226; Zablocki VA Medical Center, Milwaukee, WI 53295; and Marquette Univ., Milwaukee, WI 53233.

Estimation of lung extravascular water volume (Q_{ew}) using the multiple indicator dilution method with a hydrophilic indicator such as ^{3}HOH, along with a vascular reference indicator, can be equivocal if localized regions of the lung are unperfused. A possible solution would be to use both hydrophilic and lipophilic indicators assuming that the extravascular volume of distribution for the lipophilic indicator would be independent of Q_{ew}. We found in isolated perfused dog lung lobes that the extravascular volume of distribution (Q_{ed}) for the lipophilic amine ^{14}C-diazepam, was inversely proportional to the albumin concentration of the perfusate, and, with no protein in the perfusate, it was much larger than Q_{ew}. This suggested that the diazepam was virtually excluded from the aqueous fractions of both the lung and the perfusate. With 5% albumin in the perfusate the ratio $R=Q_{ew}/Q_{ed}$ was 0.60 ± 0.15 (SE) in the normal lobes. When the lobes were made edematous, Q_{ew} increased by 41.9 ± 9.8% and R increased to 0.80 ± 0.05. When lobes were made edematous and localized obstruction produced by embolization, Q_{ew} decreased by 53.5 ± 7.8%, but R still increased to 1.01 ± 0.08. These results suggest that an increase in R indicates edema around perfused vessels even when the measured Q_{ew} decreases due to a decrease in the fraction of the lung that is perfused.

Supported by the Dept. of Veterans Affairs and NHLBI 24349.

52.1

THE EFFECT OF RACE AND ACCLIMATIZATION ON COLD-INDUCED VASODILATATION OF THE FINGERS. R.G. Hoffman and L.E. Wittmers, Jr., (SPON: L.J. Heller) Hypothermia and Water Safety Laboratory, University of Minnesota-Duluth School of Medicine, Duluth MN. 55812.

Acclimatization to a cold environment has been shown to result in alteration of the peripheral vascular vasoconstriction phase of the response of the fingers to cold water. Cold-induced vasodilatation or CIVD should decrease the likelihood of cold injuries, i.e. frostbite. It has been reported, however, that vasodilatation of the fingers is a relatively rare phenomenon in Blacks, and that the fingers of Black subjects exposed to cold water cool at a faster rate than those of Caucasian subjects. These prior studies have included subjects from various geographical areas and varying degrees of prior cold exposure. In the present experiments, the index and ring fingers of 12 Black and 12 Caucasian age-matched male subjects who were all lifelong residents of Northern Minnesota were immersed in 2° C water for 30 minutes, and finger temperatures were continuously monitored as an estimate of blood flow. There were no statistically significant differences between the 2 racial groups in amount of maximum temperature drop from baseline prior to the first CIVD, elapsed time to the first CIVD, temperature rise during the first CIVD preceding the return of vasoconstriction, or elapsed time until the return of vasoconstriction. Black subjects were observed to vasodilate faster during the second CIVD than Caucasian subjects ($p< 0.05$, paired t-test). The results call into question previous assumptions regarding racial differences and suggest that geographical origin, prior cold exposure and acclimatization may be more powerful predictive variables. (Supported in part by U.S. Naval Medical Research Command Grant #N00014-88-K-0582).

52.2

TISSUE TEMPERATURE PROFILE IN THE HUMAN FOREARM DURING THERMAL STRESS.
Michel B. Ducharme, Walter P. VanHelder*, and Manny W. Radomski*
Univ. of Toronto, and DCIEM, Toronto, Ont., Canada, M3M 3B9.

The purpose of the present study was to investigate the effect of a large spectrum of water temperature (T_w from 15 to 36 °C) on the tissue temperature profile of the resting human forearm at thermal stability. Muscle temperature (T_m) was continuously monitored by a calibrated multicouple probe during 3 hours immersion of the forearm. The probe was implanted approximatively 9 cm distal from the olecranon process along the ulna ridge. T_m was measured every 5 mm, from the geometric axis of the forearm (determined from CT scan) to the skin surface. Along with T_m, skin temperature (T_{sk}), rectal temperature (T_{re}) and blood flow ($\dot{Q}$) were measured during the immersions. For all temperature conditions, the temperature profile inside the limb was linear as a function of the forearm radius ($p<0.001$). Temperature gradient measured in the forearm ranged from 0.2 ± 0.1 °C·cm^{-1} (T_w=36 °C) to 2.3 ± 0.5 °C·cm^{-1} (T_w=15 °C). The maximal tissue temperature was measured in all cases at the geometrical axis of the forearm, and was lower than T_{re}. Upon immersion at $T_w<36$ °C, the whole forearm can be considered to be part of the shell of the body. Mathematical equations were developed using these experimental data to predict, with an accuracy of at least 0.6 °C, the tissue temperature at any depth inside the forearm at steady state during thermal stress. The data of the present study support the idea of the important role of the convective heat exchange between blood and tissue on the tissue temperature of the forearm.

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52.3

SUBSTRATE AVAILABILITY AND TEMPERATURE REGULATION DURING COLD WATER IMMERSION. Lucie Martineau and Ira Jacobs *
DCIEM, Downsview M3M 3B9, and University of Toronto, Toronto M5S 1A1.

The purpose of the present study was to investigate whether alterations in the availability of both plasma free fatty acids (FFA) and muscle glycogen would impair human temperature regulation during cold water immersion. Eight seminude subjects were immersed in 18°C water on two occasions. Each immersion followed 2.5 days of a specific dietary and exercise regimen designed to elicit low (L) or high (H) glycogen concentration in large muscle groups. Nicotinic acid was administered for 2 h before and during immersion to inhibit white adipose tissue lipolysis. Biopsies from the *vastus lateralis* muscle showed that glycogen concentration before the immersion was significantly ($p<0.05$) lower for L (219 ± 17 mmol glucose • kg dry muscle^{-1}) than H (473 ± 24). However, there were no intertrial differences between the rates of glycogen utilization during cold water immersion, averaging 0.75 ± 0.15 mmol glucose • kg dry muscle^{-1} • min^{-1}. Nicotinic acid dramatically decreased plasma FFA levels in both trials, averaging 127 ± 21 µmol • L^{-1} immediately before immersion. Cold water immersion did not significantly alter those levels. Plasma glucose levels were significantly reduced following immersion in both trials, this reduction being similar in L and H (0.9 ± 0.2 mmol • L^{-1}). Mean VO_2 and RER at rest and during immersion were greater ($p<0.05$) in H than L. The calculated metabolic heat production during immersion tended to be lower ($p=0.051$) in L (15.3 ± 1.9 kJ • min^{-1}) than in H (18.5 ± 2.0). There were no intertrial differences between the immersion time, total drop of T_{re} or rate of decrease of T_{re} in L or H. These results suggest that despite marked reductions in energy substrates, body temperature was maintained through other mechanisms.

Research work supported by a grant from the Dept. of National Defence (Canada). L. Martineau is recipient of a doctoral studentship from the Fonds de la Recherche en santé du Québec.

52.4

THERMAL CONDUCTIVITY OF AIRWAY WALL: RESPONSE TO COLD.
J.M. Fouke*, A.D. Wolin*, H.F. Bowman*, and E.R. McFadden, Jr. Case Western Reserve University, Cleveland, Ohio, 44106

To determine the effects of facial cooling on intra-oral thermal events, we placed a thermal conductivity sensor on the buccal surface of the left cheek in seven normal and seven asthmatic subjects. Room temperature and cold stimuli were then applied to the integumental surface of both sides of the face while mucosal surface temperature and thermal conductivity were recorded. The room temperature challenge had no effect. However, application of the cold stimulus to the exterior of the left cheek caused a monotonic decrease in the mouth temperature in all subjects and was associated with a biphasic change in thermal conductivity, indicating that blood flow first increased and then fell. These responses were purely local in that cooling of the right side of the face did not change the temperature or blood flow on the left. No differences were noted between asthmatics and normals. The data indicate that lowering the temperature of the skin of the face produces significant alterations in the thermal environment within the mouth. With facial cooling, buccal temperature falls and blood supply rapidly rises and then decreases. This effect appears to be a purely local, thermally mediated event. Facial pressure and cutaneous reflexes do not play a role. The above changes may have profound effects on the conditioning of inspired air during oral breathing in frigid environments. (HL 33791, HL36156, SCOR HL37117, RR04288, and RR00080)

52.5

INDICES OF SKELETAL MUSCLE DISUSE IN THE HIBERNATING BLACK BEAR. J. M. Steffen and A. Koebel . Dept. Biol., Univ. Louisville, Louisville, KY 40292 and R.A. Nelson, Dept. Med., Univ. Illinois, Urbana, IL 61801.

Bears exhibit annual changes in activity, a short period of summer activity followed by prolonged hibernation. The present study examined parameters of skeletal muscle indicative of changes in contractile activity. Biopsies were obtained from the extensor hallucis longus and gastrocnemius muscles of 4 captive black bears during October (prehibernation), March (hibernation), and May (posthibernation). Samples were frozen in liquid N_2, shipped to the laboratory on dry ice, freeze-dried and ground to a powder. Aliquots were assayed for glycogen (GLY), triglyceride (TG), RNA, DNA and protein, and activities of glycolytic (PFK) and oxidative (citrate synthase) marker enzymes. Muscle GLY, TG and protein concentrations were not different between the three periods. DNA concentration in hibernation samples was increased approximately 30% ($P<.05$) compared to the other groups ($1.6\pm.2$µg/mg dry wt.), suggesting some atrophy. The RNA/DNA was depressed during hibernation; total RNA concentration was significantly ($P<.05$) elevated in posthibernation samples. These results suggest that some muscle atrophy occurs during hibernation, with an increased capacity for muscle protein synthesis observed during the posthibernation period of increased activity.

52.6

ELEVATED NOREPINEPHRINE LEVEL AND OXYGEN CONSUMPTION RATE ($\dot{V}O_2$) WITH pH-STAT ACID-BASE REGULATION DURING HYPOTHERMIA.
D.C. Willford, E.P. Hill, W. Schaffartzik*, R. Bain*, and M.C. Ziegler*. UCSD, La Jolla, CA 92093

We have previously noted that oxygen consumption rates ($\dot{V}O_2$) were unexpectedly high during hypothermia with pH-stat acid-base regulation, while oxygen consumption decreased as expected with alpha-stat regulation (The Physiologist 29:178, 1986). We have measured $\dot{V}O_2$ and other data in domestic pigs which were anesthetized, instrumented, and cooled to 29°C. Norepinephrine levels were measured in 5 of the animals to test the hypothesis that the increased $\dot{V}O_2$ values were associated with activation of the sympathetic nervous system (SNS). In the alpha-stat animals (pH 7.53 at 29°C), $\dot{V}O_2$ decreased to 73% of the normothermic values, while the norepinephrine level increased slightly (32%) over the normothermic value. In the pH-stat animals (pH 7.38 at 29°C), $\dot{V}O_2$ remained at 94% of the normothermic value, while the norepinephrine level increased over 400%.

	Temp °C	pH	$\dot{V}O_2$ (ml/min/kg)	NE pg/ml
Normothermia (10)	36.5	7.424	4.26	73.9
alpha-stat (10)	29.2	7.527	3.12	97.5
pH-stat (7)	29.2	7.381	4.00	304.5

We suggest that maintaining pH at 7.4 during hypothermia activates the SNS leading to an increase in $\dot{V}O_2$.
Support: HL 17731 and the Parker B. Francis Foundation.

52.7

SPLANCHNIC SYMPATHETIC NERVE ACTIVITY IN THE HEAT-STRESSED RAT. Carl V. Gisolfi, Ronald D. Matthes and Kevin C. Kregel. University of Iowa, Iowa City, Iowa 52242.

Previous work from our laboratory has shown a selective loss of splanchnic vasoconstriction with severe hyperthermia in the rat (JAP 64:2582, 1988). In a subsequent study, celiac ganglionectomy significantly increased heating rate, reduced heat tolerance time, and eliminated the rise in mesenteric resistance with heating (JAP 66:1359, 1989). The purpose of this study was to quantitate sympathetic nerve activity (SNA) from the greater splanchnic nerve during heat exposure of the anesthetized (sodium pentobarbital, 50 mg/kg) and artificially respired animal. Mean arterial pressure (MAP), splanchnic SNA, and colonic temperature (T_c) were recorded. T_c was elevated from 37.9±0.77°C to 42.4±0.77°C in 69.4±0.6 min by increasing ambient temperature to 38°C in an environmental chamber. Splanchnic SNA was 51±15 impulses/min at a T_c of 37°C and increased significantly as T_c exceeded 40°C ($p<0.05$). At the termination of the experiment (MAP<60 mmHg), when T_c averaged 42.4±0.77°C, splanchnic SNA was 262±41 impulses/min. Control animals maintained at a T_c of 37-39°C for a time period comparable to the duration of heating showed no change in SNA from baseline values. We conclude that the decline in superior mesenteric vascular resistance in the hyperthermic rat observed in previous studies can not be attributed to a decline in SNA. Supported by NIH Grant HL 38959.

52.8

ADAPTIVE CHANGES IN SWEATING ACTIVITY OF ELDERLY WOMEN. M.K. Yousef and N. Ohnishi*. Dept. Bio. Sci., Desert Bio. Res. Cntr., Univ. of Nevada, Las Vegas, NV 89154.

Heat acclimation increases sweating in young men and women. However, few studies have examined this relationship in the elderly. The effects of daily exposure of one arm to a warm water bath on sweat activity and other related responses were examined in young and old women. The left arm sweat glands were trained locally by repeated immersion for 2 hr daily in 42C for 14 consecutive days. Measurements were made on 8 young ($\bar{X}$=23.8yr) and 7 old ($\bar{X}$=70.7yr) women and included: arm sweat volume (ASV), arm onset of sweating (AOS), total body sweat rate (BSR), arm skin blood flow (SKBF), heart rate (HR) and rectal temperature (TRE). Measurements were taken one day prior to the immersion sequence and again on the day after training procedure by immersion of both legs in a 42C water bath for 80 min. Post training, ASV increased 134 and 155%, respectively. However, AOS and BSR did not change in either age group. The % increase in SKBF was greater in the young after 40 min immersion but at 80 min, it was the same in both groups. The HR increased 34 and 22 beats/min and Tre increased 0.34 and 0.65 in the young and old, respectively. Although sweat gland activity increased significantly in response to heat acclimation in elderly women, the % increase was greater in the young. Optimum vasodilatation was delayed in the elderly, leading to a greater rise in Tre. (Supplied in part by UNLV Research Council).

NEUROENDOCRINES/REPRODUCTION/AGING

53.1

OXYTOCIN (OT) MODULATES RELEASE FROM OT-NEURONS BUT NOT FROM VASOPRESSIN (VP)-NEURONS IN CONSCIOUS RATS.
Savio W.T. Cheng* and William G. North* (SPON: Heinz Valtin) Dartmouth Medical School, Hanover, NH 03756.

We examined the effects of peripherally administered oxytocin on release from oxytocin-neurons and from vasopressin-neurons as indexed by plasma concentrations of oxytocin-associated neurophysin, [OT-RNP], and vasopressin-associated neurophysin, [VP-RNP], under basal conditions, and under conditions of high plasma osmolality induced by acute salt-loading. Studies were performed on conscious, chronically instrumented Long-Evans rats. Oxytocin (1 µg or 10 µg) dissolved in 1 ml of 0.9% saline was administered intraperitoneally to animals 1 h before they received an intravenous infusion of hypertonic saline over 60 min at a rate designed to raise plasma osmolality by approximately 0.75 mOsm/min. Intraperitoneal (IP) injection of 1 µg oxytocin did not significantly alter basal plasma osmolality (Posm), [OT-RNP], [VP-RNP] or mean arterial pressure (MAP). Basal Posm was lowered (300 ± 2 to 291 ± 2 mOsm/kg H_20, $p<0.001$) and MAP raised (124 ± 3 to 142 ± 5 mmHg, $p<0.02$) by 10 µg oxytocin. However, there were no significant changes in basal [OT-RNP] and [VP-RNP] induced by this dose of oxytocin. Administration of 1 µg oxytocin significantly enhanced (> 2 times) the responsiveness of oxytocin-neurons to acute salt-loading as indicated by the slope of the relationship between Δ[OT-RNP] and ΔPosm (38.3 versus 15.7 fmol·ml^{-1}·mOsm^{-1}·kg). In contrast, the slopes of the relationship between Δ[VP-RNP] and ΔPosm for the groups receiving pretreatment with 1 µg oxytocin, 10 µg oxytocin and vehicle were similar (7.4, 7.4 and 6.3 fmol·ml^{-1}·mOsm^{-1}·kg). Surprisingly, administration of 10 µg oxytocin did not appear to alter the rise in [OT-RNP] with Posm (11.8 fmol·ml^{-1}·mOsm^{-1}·kg versus 15.7 fmol·ml^{-1}·mOsm^{-1}·kg for controls). Our data implies that oxytocin can enhance release from oxytocin-neurons under stimulated conditions, but has no effect on basal or stimulated release from vasopressin-neurons.

53.2

EFFECT OF CALCITONIN ON THE BRAIN CHOLINERGIC ENZYMES. E.T. Oriaku* and K.F.A. Soliman. College of Pharmacy and Pharmaceutical Sciences. Florida Agricultural and Mechanical University, Tallahassee, FL 32307.

In this experiment rats were randomly divided into two groups. The control group was given saline while the other group was administered iv 10 IU/kg of thyrocalcitonin. Before hormone administration and 15, 30, 90, and 120 minutes after treatment, analgesia was measured. Moreover, after 120 mins, animals were sacrificed by decapitation and their brains were removed and dissected into cerebral cortex, hypothalamus, thalamus and the pons. Acetylcholinesterase (AChE) and Choline Acetyltransferase (ChAT) activities were measured in each brain region. Results of this experiment indicated that there was significant ($P<0.01$) analgesia up to 90 mins after drug administration. There was also a significant ($P<0.01$) increase in ChAT activity in the thalamus and the pons with no significant changes in the other tissues studied. There was a significant ($P<0.01$) increase in AChE activity of the cerebral cortex and a significant decline in ChAT activity of the thalamus ($P<0.05$) and the pons ($P<0.01$). It was concluded from this study that brain cholinergic system might be involved in calcitonin-induced analgesia. (Supported by a grant from NASA NAG 2-411 and NIH grants RR 0811 and RR 03020)

53.3

GLUCOSE-INDUCED ANALGESIA OF GENETICALLY OBESE RATS. C. Goodman* and K.F.A. Soliman. College of Pharmacy, Florida A&M University, Tallahassee, FL 32307.

Obese male Zucker rats and their lean littermates (19-22 weeks old), kept under controlled environmental conditions were used in this experiment. In the first experiment animals were treated with glucose (10g/kg) for two days and pain measurements were taken prior to an at 15, 30, 60 and 120 minutes after glucose administration. In pain measurements the tail flick, hot plate and hind paw pressure methods were used. The results indicate that the administration of glucose was associated with profound analgesia in both groups using the tail flick and the hot plate procedures. Repeated administration of glucose in the second day was accompanied by the development of tolerance to glucose-induced analgesia in both groups. Obese animals were found to develop more tolerance to glucose than their lean littermates. Similar results were obtained when morphine (10mg/kg) was used. Moreover, the administration of morphine was associated with more than a 200% increase in glucose levels at 120 minutes. Treatment with naloxone (5mg/kg) resulted in hyperalgesia using the tail flick and hot plate in both obese and lean animals. However, using the hind paw pressure test, only the obese animals showed hyperalgesia. The results of these experiments might indicate the involvement of opioid receptors in glucose-induced analgesia. (Supported by NIH grants RR0811, RR03020 and NASA grant NAG 2-411)

53.4

BRAIN BIOGENIC AMINES INVOLVEMENT IN VAGINAL STIMULATION-INDUCED ANALGESIA. J.V. Lee* and K.F.A. Soliman. College of Pharmacy, Florida A&M University, Tallahassee, FL 32307.

Female Sprague-Dawley rats were ovariectomized and two weeks later hormones were administered. The first group was primed with 5ug of estrogen without stimulation while another had the same treatment but was vaginally stimulated. A third group received estrogen and 48 hrs later were treated with 5mg progesterone and without stimulation, while another group with the same treatment was stimulated. Animals were sacrificed and specific brain regions were assayed for norepinephrine (NE) epinephrine (EP), dopamine (DA), serotonin (5HT) and 5-hydroxyindoleacetic acid (5HIAA). Results indicate that vaginal stimulation was associated with analgesia and a significant increase in 5HIAA of the hypothalamus. In the hippocampus there was a significant increase in NE, DA and 5HIAA as compared to the control group. Meanwhile, there was an elevation of epinephrine and 5HT levels in the midbrain after vaginal stimulation. There were significant increases in 5HT and 5HIAA contents of the pons after vaginal stimulation. It was concluded from this study that vaginal stimulation was associated with changes in 5HT or 5HIAA in all brain regions examined which might indicate the involvement of 5HT in vaginal-stimulation induced analgesia. (Supported by NIH grants RR 0811, RR 03020 and NASA grant NAG 2-411).

53.5

EFFECT OF TJ-23 ON LHRH AND LH SECRETION IN RATS. Tokao Koyama* N. Hagino, Kenji Sakamoto* and Norma E. Gonzalez*. The University of Texas Health Science Center at San Antonio, Texas 78284.

We have reported that administration of TJ-23 in immature female rats increases catocholamines in the brain and facilitates the ovarian estrogen output and increases uterine estrogen receptors. Furthermore, it was found that an anesthetization of the hypothalamus with nembutal during the critical period of LH surge in TJ-23 treated rats blocks ovulation. It seems likely that TJ-23 may have the neuroendocrine effect on ovulation and thus may bring precocious ovulation in immature rats. Therefore, further experiment was designed to examine if TJ-23 has the effect on LHRH and LH secretion. Immature female rats (Sprague-Dawley albino) were housed in controlled lighting and temperature. TJ-23 (500mg/kg body weight in drinking water) was given on 23 days of age and continued for either 7 or 10 days. The LHRH in the hypothalamus and LH in the anterior pituitary and serum were assayed by RIA. It was found that treatment with TJ-23 resulted in an increase of both LHRH and LH on 29 days of age, but they were decreased on 33 days of age. However, in this experiment we did not expect to see any significant change of serum LH, because all of the animals were sacrificed prior to LH surge in order to determine the LHRH and LH. From previous studies and present experiment, it is concluded that TJ-23 has the neuroenodcrine effect on ovulation; TJ-23 moderates both LHRH and LH secretion. Therefore, TJ-23 facilitates the neuroendocrine chain of events on ovulation. (The study was supported by grant and training grant from Tsumura & Co.)

53.6

EFFECT OF CHRONIC TREATMENT WITH TOKISHAKUYAKU SAN (TJ-23) ON LHRH, LH AND FSH IN THE HYPOTHALAMUS IN THE EARLIER PROCESSING OF AGING IN RATS. N. Hagino, Kenji Sakamoto*, Shuichi Sakamoto* and Norma E. Gonzalez*. The University of Texas Health Science Center at San Antonio, Texas 78284.

We have reported that treatment with TJ-23 in the earlier processing of aging in the female rats unlocks the refractoriness of the ovarian cyclicity and restores the cyclic appearance of estradiol peak in serum which is associated with estrous cycles. Histology of the ovary in TJ-23 treated females revealed the maturation of follicles with healthy corpus luteum. These findings suggest that TJ-23 arouses the neuroendocrine controlled pituitary ovarian function and thus may unlock the refractoriness of the ovarian cyclicity. Therefore, the study was designed to examine if TJ-23 has the neuroendocrine effect in the earlier processing of aging. TJ-23(500mg/Kg body weight) was given daily through drinking water on 200 days of age and continued for three months. Treated Sprague-Dawley albino female rats exhibited estrous cycles, but nontreated females demonstrated persistent estrus. After completion of experimental sessions, the hypothalamus and the anterior pituitary were dissected for assay LHRH, LH and FSH using RIA. Treatment with TJ-23 tended to decrease LHRH in the hypothalamus (56.5 ± 13.4 in TJ-23 treated group vs 102.5 ± 25.2 pg/mg in control group), however, statistical analysis revealed the borderline of change. A remarkable observation made in this study was that treatment with TJ-23 resulted in a decrease of hypothalamic contents of FSH (221.8 ± 101.8 in TJ-23 treated group vs 675.8 ± 156.3 pg/mg in control group $p<0.05$). No change of hypothalamic LH and anterior pituitary FSH and LH was observed. It seems likely that an increase of hypothalamic FSH in the earlier processing of aging may be associated with the refractoriness of the ovarian cyclicity. Therefore, a decrease of hypothalamic FSH by treatment with TJ-23 seems to bring a restoration of ovarian cyclicity in the earlier processing of aging. (The study was supported by grant and training grant from Tsumura & Co.)

53.7

EFFECT OF CHRONIC TREATMENT WITH TOKISHAKUYAKU-SAN (TJ-23) ON CHOLINE ACETYLTRANSFERASE IN THE EARLIER PROCESSING OF AGING IN RATS. Shuichi Sakamoto*, N. Hagino, Kazuo Toriizuka*, Norma E. Gonzalez*, Hajime Hamada* and Takao Koyama* The University of Texas Health Science Center at San Antonio, Texas 78284.

It has been reported that administration of TJ-23 in rats improves the memory related behavior (the recognition of the space). It suggests that TJ-23 may moderate the cholinergic activity of both septo-hippocampal system and basal forebrain-cerebral cortical system. Therefore, the study was designed to examine if TJ-23 has the effect on the cholineacetyltransferase. Sprague Dawley albino female rats in the earlier aging processes were used for this study. TJ-23 (500mg /kg body wt) was given daily through drinking water on 200 days of age and continued for three months. The brain were removed from the skull upon the completion of the experiment and placed in liquid nitrogen immediately. The areas of the septum and diagonal band of Broca (Septo-DBB), hippocampus, amygdale and cerebral cortex were dissected, and the activity of cholineacetyltransferase (ChAT) was assayed using 14C-acetyl-CoA as the substrate. It was found that treatment with TJ-23 resulted in a decrease of the ChAT activity in the cerebral cortex (13.1 ± 1.0 in TJ-23 treated group vs 15.6 ± 1.15 pM/μg protein in control group $p<0.01$), and treatment with this regimen influenced the ChAT activity in the septo-DBB. However, we have yet found any significant changes of the ChAT activity in both the hippocampus and amygdala. From the observation was made on this experiment, it infers that TJ-23 has the effect on the synthesis of acetylcholine in the earlier aging processes of rats. It implies that treatment with TJ-23 would improve the memory related behavior (the recognition of the space). (The study was supported by grant and training grant from Tsumura & Co.)

53.8

EFFECT OF CHRONIC TREATMENT WITH TOKISHAKUYAKU-SAN (TJ-23) ON THE NICOTINE ACETYLCHOLINE RECEPTORS IN THE EARLIER PROCESSING OF AGING IN RATS. Kazuo Toriizuka*, N. Hagino, Shuichi Sakamoto*, Norma E. Gonzalez*, Hajime Hamada* and Takao Koyama. The University of Texas Health Science Center at San Antonio, Texas 78284.

We have reported that when young female rats were treated with TJ-23 for one week, treatment with this regimen stimulates the synthesis of nicotine acetylcholine receptors and catecholamines in the cerebral cortex and hippocampus. However, it was found that treatment with TJ-23 for three months in the earlier processing of aging stimulates the synthesis of dopamine in the cerebral cortex, but not in the hippocampus. Therefore, the study was designed to examine if chronic treatment with TJ-23 stimulates the synthesis of nicotine acetylcholine receptors (nAchRs) in the cerebral cortex. TJ-23 (500mg/kg body wt) was given daily through drinking water on 200 days of age and continued for three months in the Sprague-Dawley albino female rats. After completion of experimental sessions, brains were dissected for assay for nAchRs. It was found that chronic treatment with TJ-23 resulted in an increase of nAchRs in the cerebral cortex, but not in the hippocampus. From the observation was made in this study, it seems likely that chronic treatment with TJ-23 stimulates the activity of nAchRs and subsequently thus facilitates the synthesis of dopamine in the cerebral cortex. (The study was supported by grant and training grant from Tsumura & Co.)

53.9

MALE REPRODUCTIVE ORGANOMEGALY IN RATS RECOVERING FROM EARLY HYPOTHYROIDISM. Paul S. Cooke* and Esmail Meisami, Depts. of Veterinary Biosciences and Physiology & Biophysics, University of Illinois, Urbana, IL 61801

We previously found that growing rats, recovering from early postnatal hypothyroidism, had markedly enlarged testes (Meisami et al., Fed. Proc. 45:177,'86). In the present study we examined growth and histology of other male organs and measured testosterone (T) levels in these animals. Male rats were given the goitrogen PTU (6-n-propyl-2-thiouracil, 0.1% in drinking water) from birth until day 60, then allowed to recover by withdrawal of PTU. At 9 months of age, the animals were killed and serum was collected for T assay. The testes, epididymides, seminal vesicles and ventral prostate were weighed and processed for histology or DNA assay. Body weight in recovering animals was 20% less than in controls, while testicular weight and DNA content were approximately 90% greater (mean wet wt:3.74± 0.06 vs. 1.91± 0.07 g in controls; n=6 for each). Mean wet weight and total DNA content of the epididymis, seminal vesicle and prostate in the recovering animals were increased by 55%, 77% and 93%, respectively; DNA concentrations were however unchanged. Histology of all organs from the recovering animals indicated no abnormalities, while T levels were more than doubled (3.43 vs. 1.60 ng/ml). These results indicate that recovery from early hypothyroidism is accompanied by a marked overgrowth of the male reproductive organs. Possible mechanisms of this overcompensatory growth response are under investigation.

53.10

VASECTOMY REDUCES LUMINAL FLUID pH IN RAT TESTIS AND EPIDIDYMIS IN VIVO. C.R. Caflisch and T.D. DuBose, Jr. Department of Internal Medicine, Physiology and Biophysics, University of Texas Medical Branch, Galveston Texas 77550.

Previous studies have demonstrated that short term vasectomy is associated with impaired water reabsorption in the initial segment of the rat epididymis. Since the initial segment is a site of acidification of luminal fluid, impairment of water reabsorption could alter substantially luminal fluid pH. In this study, the effect of bilateral vasectomy on luminal acidification was assessed in rat seminiferous tubules (ST), initial segment (IS), proximal caput (PCP), middle corpus (MCR), and proximal cauda epididymidis (PCD) by determination of in situ pH with glass membrane double barreled pH microelectrodes. Five Sprague-Dawley rats received bilateral vasectomy (BV) and were prepared for micropuncture after 8 weeks. Five rats served as sham-operated (SO) controls. pH values at each micropuncture site were (mean + SEM):

	ST	IS	PCP	MCR	PCD
SO	6.90±.02	6.85±.04	6.57±.03	7.15±.03	6.81±.02
BV	**6.73±.02	*6.68±.04	6.54±.02	**6.95±.05	6.85±.06

*P<0.02 vs SO, **P<0.005 vs SO

Thus, pH of luminal fluid in the ST, IS and MCR was significantly more acid after vasectomy of 8 weeks duration. These findings are compatible with impairment of acid-base, as well as water transport pathways after vasectomy.

53.11

RAPID VASCULAR ESCAPE AND HEPATIC CLEARANCE OF [123I]-16alpha-IODOESTRADIOL DEMONSTRATED BY GAMMA CAMERA PLANAR IMAGING. Anton Scharl*, John A. Holt, Richard J. Baranczuk*, Peter G. Pryde*, David F. Preston*. University of Chicago, Chicago, IL 60637, Biomedical Products, Overland Park, KS 66204, University of Kansas, Kansas City, KS 66103.

Auger electron emitting estrogen receptor (ER) ligands may be useful against ER-rich malignancies. [123-I]16alpha-iodoestradiol ([123-I]E) (Its gamma emissions allow imaging.) was used for biodistribution studies in juvenile female pigs and superovulated rabbits whose reproductive tracts served as models for ER-rich intraperitoneal cancer. Seven pigs received 0.6-1.3 mCi [123-I]E *i.p.*. Body fluids were sampled at regular time intervals until the animals were killed after 2 - 3 hr. We found that 50% to 75% of the radiotracer is cleared from the peritoneal cavity within 30 min and passes in the urine within 3 hr. Within 20 min after *i.p.* infusion, the amount of [123-I]E in blood peaked to a maximum of 8%-10% of the injected dose. Three hr after infusion, the ER-rich reproductive tract had uptake of 0.083% of the injected dose/g tissue (>63:1 over blood). Retention of the radiopharmaceutic in non-target organs (ER poor) was below 0.008%/g with exception of the spleen (0.022%/g) and omentum (0.08%/g). Prior treatment with antiestrogen and cold E blocked only the reproductive tract uptake reflecting specificity of the [123-I]E for ER. Whole body planar imaging was performed on rabbits 2 min to 18 hr after *i.a.* injection of [123-I]E. Within 2 min we observed that the radiotracer escapes the circulatory system; this was confirmed by comparison with [99Tc]-labeled red blood cells. Further pharmacokinetics could be observed by imaging as the radiopharmaceutic was cleared through the liver into the gall bladder and proximal intestine. **COMMENT:** Whole body imaging of a radiohalogenated ER ligand provided unexpected insight into the pharmacokinetics of a radiopharmaceutic that were not readily apparent by tissue counting and fluid sampling. By combining the information available from imaging with that from tissue and fluid sampling a more accurate assessment of pharmacokinetics for dosimetry is achieved than with either alone. [Supported in part by CA-27476 (JAH) and SBIR-CA-36733 (RJB).]

RENAL PHYSIOLOGY

54.1

CARBONIC ANHYDRASE(CA)-II DEFICIENT MICE: RENAL FUNCTION AND RESPONSE TO INHIBITION. W.F. Brechue, E. Kinne-Saffran,* R.K.H. Kinne and T.H. Maren.* University of Florida, Gainesville, FL 32610 and Max-Planck-Institut, Dortmund, FRG.

Mice carrying a Car 2^b null mutation were produced; homozygotes for the new allele lacked (CA)-II (Lewis et al., Proc Natl Acad Sci 85, p. 1962). Renal function, response to CA inhibition (CAI), and food restriction acidosis were studied in 3 groups of mice; CA-II deficient (CAD), heterozygous litter mates (LM) and normal Swiss-Webster (SW). Baseline rates of urinary (UR) Na^+ and K^+ excretion were similar in all groups, but UR Cl^- and HCO_3^- were higher in CAD. UR pH was 6.27 in SW, 6.33 in LM and 7.15 in CAD. CAI led to similar increments in UR Na^+, K^+, HCO_3^-, pH, and flow in all three groups but had no effect on Cl^- output. Food restriction led to equivalent reductions in UR pH in all groups of about 0.5 units; CAD maintained their relative higher pH. Renal CA activity was determined in isolated brush border membranes (BBM) and in cytosolic (CYTO) fractions from cortex, medulla and papilla. LM and SW mice showed similar CA activity in all fractions, but CAD lacked CA activity in cortical, medullary and papillary CYTO. However, normal CA activity was found in BBM of CAD. This enzyme showed sulfonamide sensitivity similar to CA-IV. In conclusion, in CAD mice there appears to be an acidification defect in the distal tubule, correlating with a lack of CA activity in CYTO from distal segments. However, proximal tubule function is maintained, in the absence of CYTO CA-II, by the BBM bound enzyme.

54.2

THE PHYSIOLOGICAL ROLE OF RENAL KALLIKREIN. M. Marin-Grez* and P. Odigie* (SPON: K. Thurau) Dept. of Physiology, University of Munich, FRG.

We have investigated changes of kallikrein (Kal) activity in renal cortex (RK) and of its urinary excretion rate (UK) in rats. Desoxycorticosterone (15 mg/kg.day) increased UK, without affecting RK. Trichlormethiazide (0.25 mg/kg.min), a blocker of connecting tubule (CNT) cell NaCl co-transport, reduced UK. Kal release from rat kidney slices was lowered by dihydro-ouabain (10^{-3} M). Thus, Kal secretion into the tubular fluid depends on NaCl reabsorption. In anesthetized normal rats, UK correlates to filtered Cl^- (r:0.62, p<0.0007) but not Na^+ or K^+. The excretions of these ions were not correlated to UK. An inverse multiplicative relationship was found between Kal and bicarbonate excretion (r:-0.72, p<0.002) in anesthetized normal and Na depleted rats. These parameters were also correlated in awake animals (r:-0.99, p<0.0002). When purified Kal was added to the perfusate of isolated perfused kidneys a highly significant inverse relationship between UK and bicarbonate excretion was found (r=-0.78, p<0.00001). Thus, Kal release depends on NaCl reabsorption by CNT cells and the physiological role of this enzyme is to regulate bicarbonate excretion.

54.3

RAPID POTASSIUM ADAPTATION IN THE RAT. Cynthia A. Jackson and L. Rabinowitz, Univ. of Calif., Davis, CA 95616

After several days on an intake of a high K diet, the renal excretion of an intravenous K load is enhanced. The present experiments were performed to determine if a similar renal K adaptation was produced within hours of intake of a normal K ration. Rats maintained in a 12 h light-dark environment were either allowed access to a standard chow diet (FED) or had food removed prior to the onset of the dark phase to prevent the early dark phase ingestion (FASTED). Three hours into the dark phase, both groups were anesthetized and one h later, the fed (stomach contained food) and the fasted (stomach empty) rats were infused with 0.143 M KCL, i.v. Control fed and fasted rats did not receive any KCl. The U_KV (6.36 μeq/min) and P_K (3.96 meq/l) in the control fed rats were greater than the U_KV (3.94 μeq/min) and P_K (3.18 meq/l) in the control fasted rats. During the KCl infusion for 100 minutes, the U_KV increased to 9.98 μeq/min in the fed rats and 9.17 μeq/min in the fasted rats. Change in the P_K (ΔP_K) in the fasted rats (2.69) was greater than in the fed rats (1.26). Consequently, $\Delta U_KV/\Delta P_K$ was greater in the fed rats (3.46 μeq/min per meq/l) than in the fasted rats (2.32 μeq/min per meq/l). At any level of P_K, the U_KV was higher in the fed group than in the fasted group. This relationship was not altered by concurrent infusion of canrenoate (an aldosterone antagonist), somatostatin (insulin secretion inhibitor), or a NaCl-mannitol diuresis. These results indicate that within 3-6 hours following a normal oral K intake, the renal excretion of an i.v. K load is enhanced. This rapid renal K adaptation is not dependent on concurrent levels of P_K, aldosterone, insulin or $U_{Na}V$. These results support our previous suggestion that K adaptation is a rapid process that may involve an unidentified kaliuretic regulatory factor and enteric and/or splanchnic K receptors.

54.4

EFFECT OF GH-RELEASING FACTOR ANTAGONIST ON Na, K, AND Pi BALANCE IN IMMATURE RATS. Susan E. Mulroney, Michael D. Lumpkin* and Aviad Haramati. Georgetown Univ. Sch. of Med., Washington, DC 20007.

It is known that young animals maintain a positive balance for minerals and electrolytes to facilitate proper growth and development. We recently reported that a newly-described peptidic antagonist to growth hormone-releasing factor (GRF-AN:[N-Ac-Tyr^1-Arg^2]-GRF-(1-29)-NH_2) suppressed the pulsatile release of growth hormone (GH), and reduced somatic growth in immature rats. In the present study we evaluated whether suppression of GH release is also associated with changes in Na, K, and Pi homeostasis. Immature male Wistar rats (4-4.5 wks) were implanted with Silastic jugular cannulae and placed in metabolic cages. Control urine and fecal samples were obtained, and then rats were given iv injections of either saline vehicle or GRF-AN (100 ug/kg) twice daily for 4 days. Animals receiving saline vehicle grew 24±3% over the 4 experimental days, while GRF-AN rats grew only 5±2%. Net retention of Na, K, and Pi on the control day was the same in both groups (Na, 55±8 vs 60±3%; K, 42±10 vs 43±4%; Pi, 54±7 vs 53±3%, for saline control and GRF-AN groups). However, rats receiving GRF-AN had reduced retention for all electrolytes after only one day, and remained at the decreased level throughout the treatment (Average net retention over 4 experimental days in GRF-AN vs saline control rats: Na, 2±5* vs 60±2%; K, -13±6* vs 48±4; Pi, 32±2* vs 59±3, *=P<0.01). The decrease in retention in each case was attributed an increase in urinary, but not fecal excretion of electrolytes. Thus, GH, directly or indirectly, may play and important role in the growth process by promoting renal Na, K, and Pi retention.

(Work supported by NIH DK-36111 to A.H.)

54.5

EFFECT OF PROTEIN KINASE C (PKC) INHIBITION ON THE RENAL RESPONSES TO CALCITONIN (CT) AND PARATHYROID HORMONE (PTH) IN THE RAT. T. J. Berndt*, Y. Kinoshita†, and F. G. Knox, Mayo Medical School, Rochester, MN 55905

Recent in vitro studies suggested that PKC may be involved in renal phosphate (P) regulation. The present study determined whether infusion of H-7, an inhibitor of PKC, blunts the phosphaturic response to CT OR PTH in vivo. Clearance studies were performed in acutely TPTX rats fed a normal P diet. Vehicle (0.9% NaCl) or H-7 (400 μM) were infused at 3 cc/hr into the aorta above the renal arteries. Control clearances were taken after a 2-hr equilibration period. CT, 0.3 U/kg/min

	NaCl (n=5)		H-7 (n=6)	
	C	CT	C	CT
FE_P%	0.4±0.2	9.4±3.1*	1.8±0.3	8.1±2.2*
FE_{Na}	0.9±0.4	2.1±0.5*	1.0±0.3	1.3±0.5

PTH, [1]0.1 U/kg/min; [2]1 U/kg/min

	NaCl (n=4)			H-7 (n=5)		
	C	PTH[1]	PTH[2]	C	PTH[1]	PTH[2]
FE_P%	1.4	13.8	34.6*	1.9	16.1*	35.4*
±SE	0.7	2.5	2.7	±1.4	±4.5	±1.9

FE, fractional excretion; p<0.05, paired t

We conclude that intraortic infusion of H-7, a PKC inhibitor, blunts the natriuretic effect of CT, but does not affect the phosphaturic response to CT or PTH.

54.6

TRANSPORT OF ENALAPRILAT ACROSS BASOLATERAL AND LUMINAL MEMBRANES OF RAT KIDNEY TUBULAR CELLS. Andreas J. Schwab*, Inés A.M. de Lannoy*, Carl A. Goresky, and K. Sandy Pang*. McGill Univ. Medical Clinic, Montreal Gen. Hosp., Montreal, Que. H3G 1A4, and Fac. of Pharmacy and Dept. of Pharmacology, Univ. of Toronto, Toronto, Ont. M5S 2S2

The angiotensin-converting enzyme inhibitor enalaprilat (EA) is formed *in vivo* in liver and kidney by esterolysis of the antihypertensive drug enalapril. To promote understanding of renal elimination of EA, we performed multiple-indicator dilution experiments in the isolated perfused rat kidney. Kidneys were perfused single-pass with amino-acid supplemented Krebs-Henseleit buffer containing 20% bovine red blood cells and 4% bovine serum albumin at a flow rate of 0.14 ± 0.03 ml/s per g. A bolus of ^{51}Cr-labeled red blood cells, ^{125}I-labeled albumin, L-[^{14}C]glucose, and [^{3}H]EA was injected into the renal artery, and timed samples of venous blood (up to 1 min) and urine (up to 5 min) were collected. The data were analyzed using a variable-transit-time space-distributed model (Goresky et al., *J. Clin. Invest.* 52:991–1009, 1973) with modifications accounting for glomerular filtration and the observed 15% protein binding. The glomerular filtration rate (GFR) estimated from L-glucose clearance was 9.7% ± 2.8% of total plasma flow. The ratio of renal clearance of unbound EA to GFR was 1.56 ± 0.29, indicating both glomerular filtration and net tubular secretion of EA. Unidirectional influx from plasma to tubular cells exceeded net tubular excretion by a factor of 3.35 ± 0.07. Thus, only 33% of EA taken up by tubular cells was excreted into urine, the remainder refluxing into the capillary bloodstream, indicating bidirectional permeation of EA across the basolateral membrane. Supported by grants from MRC (Canada) and NIH.

54.7

DISSOCIATION OF RENAL INTERSTITIAL HYDROSTATIC PRESSURE (RIHP) AND THE NATRIURESIS OF ATRIAL NATRIURETIC FACTOR (ANF). A. A. Khraibi, D. M. Heublein*, J. C. Burnett, Jr., and F. G. Knox, Mayo Clinic, Rochester, MN 55905

These experiments tested the hypothesis that the natriuretic effect of ANF is mediated by increases in RIHP in anesthetized rats. In both groups of Wistar rats used in this study, one kidney was acutely decapsulated and the contralateral kidney was used as control. Renal decapsulation was used to control RIHP. In one group, 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of synthetic ANF was infused i.v. This pharmacologic dose of ANF produced a significant increase in RIHP of the control kidney from 9.5 ± 0.8 to 11.1 ± 1.3 mmHg (p<0.05), but not in the decapsulated kidney (from 7.1 ± 0.6 to 8.1 ± 0.9 mmHg, NS). However, the changes in fractional excretion of sodium (FE_{Na}) and urine flow rate (V) were similar in both kidneys. In the second group, 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of synthetic ANF was infused i.v. This physiologic dose of ANF produced no significant increases in RIHP of decapsulated or control kidneys and the increases in FE_{Na} and V were similar in both kidneys. Thus, ANF infusion produces a significant increase in RIHP only in pharmacologic doses. When this increase in RIHP is prevented by acute renal decapsulation, and during the infusion of a physiologic dose of ANF, the natriuresis and diuresis still occurs in a similar degree. We conclude that elevations in RIHP are not essential for the ANF-induced natriuresis and diuresis.

54.8

EFFECT OF VERAPAMIL ON RENAL PROSTAGLANDINS IN VIVO AND IN VITRO. V. Lahera*, M.G. Salom*, M.L. Biondi*, R.J. Bolterman*, M.J. Fiksen-Olsen* and J.C. Romero. Mayo Foundation. Rochester, MN 55905.

The intrarenal infusion of Verapamil(5μg/Kg/min) in the presence or absence of Indomethacin (10 μg/kg/min) was studied in dogs. Verapamil, increased (p<0.05) the urinary PGE2 (from 1954 ± 530 to 7988 ± 4074 pg/min), urinary 6 keto-PGF1α (from 1916 ± 368 to 3865 ± 769 pg/min), urine flow (from 220 ± 40 to 1780 ± 450 μl/min), and sodium excretion rate (from 50.4 ± 8.8 to 308 ± 69 μEq/min). Only urinary 6-keto-PGF1α excretion was reduced with the administration of both Verapamil + Indomethacin, while the other parameters remained elevated (p<0.05). The effects of Verapamil (10^{-5}M) on PG synthesis in canine renal medullary slices and renal artery rings were determined with and without Indomethacin (10^{-5}M). Verapamil had no effect on PGE2 or 6-keto-PGF1α production, while Indomethacin reduced (p<0.05) the PG production in both preparations. Similarly, when Verapamil was added in the presence of Indomethacin, the reduction in PG production was not changed. Since Verapamil in vitro has no effect on PG production, the increase in urinary PGE2 and 6-keto-PGF1α observed during the intrarenal infusion of Verapamil might be secondary to increased urine or medullary flow.

54.9

EVALUATION OF SPONTANEOUS RENAL AUTOREGULATION IN CONSCIOUS DOGS. R. Frankel*, P.H. Brand, A. Muhly*, F.J. Kollarits*, P.J. Metting and S.L. Britton. Department of Physiology and Biophysics, Medical College of Ohio, Toledo, Ohio 43699-0008.

It is well documented that autoregulation of renal blood flow (RBF) can be induced by imposing changes in renal perfusion pressure. Although this approach reveals properties of the kidney in response to artificial perturbations, it fails to reveal if renal autoregulation occurs spontaneously in response to natural fluctuations in systemic arterial pressure (AP). By definition, autoregulation is characterized by a relative constancy of blood flow during changes in perfusion pressure. It logically follows that autoregulation must also be characterized by a lesser variability in blood flow than perfusion pressure. Because the spontaneous fluctuations of AP and RBF in conscious dogs were poorly correlated and did not permit a reliable quantification of autoregulation, we evaluated spontaneous renal autoregulation based on the variabilities of AP and RBF. We defined renal autoregulation as a lesser variability in RBF than AP, using the coefficient of variation as the index of variability. The average RBF and AP for each heart beat was calculated in five dogs standing quietly at rest. Data were collected for about 30 minutes (2000 heart beats) on three different days for each dog (15 trials total). RBF variabilities were higher than AP variabilities in all 15 trials, indicating a lack of spontaneous renal autoregulation. In order to evaluate slower components of autoregulation, RBF and AP data were smoothed using 10, 30, 60, and 120 point moving average filters, to remove higher frequency fluctuations. Frequency domain analysis was also performed in order to detect autoregulation within any frequency range. Both methods failed to reveal spontaneous autoregulation in four dogs. One dog consistently demonstrated spontaneous autoregulation in the frequency range below 0.05 Hz. We conclude that while renal autoregulation can be artificially induced, it is generally not spontaneously expressed in conscious resting dogs. Supported by AHA and NIH (HL-01515).

63.1

USE OF COMPUTER IMAGE PROCESSING TECHNIQUES IN STUDYING CEREBRAL PERFUSION by M.Meyer*,D.Hanson*,H.Baker*,T.Yanagihara*, R.Robb Depts. of Neurology, Radiology,Physiology & Biophysics Mayo Clinic, Rochester, Minnesota, U.S.A. 55905

Using the multimodality, multidimensional biomedical image display and analysis program ANALYZE developed in the Biodynamics Research Unit at Mayo Clinic, we developed a novel and effective method for imaging cerebral perfusion in a movie format with dynamic CT scanning. After a 50cc IV bolus injection of Conray60, rapid CTs were acquired over 2 seconds every 4.3 seconds in the same 1.5mm coronal section through the sella tursica. Flow patterns not evident on the static images became evident by viewing them in a movie format. Superior registration of the static images was achieved by generating the movie by computer rather than filming the hard copy images in succession. Enhancement of the gray vs. white matter perfusion differences was achieved by using adaptive histogram equalization techniques. Further enhancement was obtained by color coding. This work demonstrates that striking computer generated movies of cerebral perfusion can be obtained non-invasively by using dynamic CT, with the additional advantage of using a relatively low dose of contrast agent at a fine section thickness of only 1.5mm.
(Video to be shown)
Supported by grants RR-2540 and HL-4664 from National Institute of Health

63.2

ULTRAFAST COMPUTED TOMOGRAPHY IN THE MEASUREMENT OF LOCAL VENTILATION PERFUSION RATIOS. David Murphy,John Nicewicz,Sal Zabbatino*,Edward Mezic, Naipaul Rambaran*,Stephanie Flicker*, Deborah Heart & Lung Center,Browns Mills, NJ 08015

Since a linear relationship exists between xenon concentration and change in density measured in Hausfield units, measurements of local ventilation V were made in a lung volume of one cc. Six normal subjects inhaled a 70% O_2/30% xenon mixture for one minute and assuming a washin curve of the form $C_t-C(1-e^{-kt})$ where K=alveolar ventilation/alveolar volume, t=time and c is concentration. Measurements of local ventilation can also be made from the washout curves assuming a form $C-Ce^{-kt}$. Scan times of 50 milleseconds permit generation of tissue time density curves so measurements of local blood flow in the same region of interest were made following a peripheral venous injection of contrast media using moment analysis. In this way calculation of V/Q ratios for local unit volumes can be made.

	V/Q RATIOS			
Subject	Right Ventral	Right Dorsum	Left Ventral	Left Dorsum
1	1.50	0.80	1.38	0.90
2	1.95	1.99	2.16	2.18
3	1.90	1.21	1.76	1.36
4	1.00	2.98	3.32	1.14
5	1.63	1.02	0.74	1.58
6	1.33	1.12	1.63	0.88
Mean	1.47	1.52	1.83	1.34

63.3

RADIOLOGIC DETERMINATION OF THORACIC GAS VOLUME, Vtg(R), IN INFANTS. E. Bar-Yishay, G. Granit*, C. Springer*, P. Mogle*, S. Godfrey*. Hadassah University Hospital, Mt Scopus, Jerusalem, ISRAEL.

We present a new method for determining Vtg(R) in infants under one year of age. The method is based on tracings of orthogonal chest X-rays as was previously applied in adults. Vtg(R) values were compared to plethysmographic determinations of lung volumes, Vtg(P), in the same infants. We studied a group of 8 apparently healthy infants and 8 with cystic fibrosis, aged 2-42 wks for a total of 19 determinations. There was no significant difference between the estimates, Vtg(R) being 168±16 ml (mean±SEM) and Vtg(P) 167±15 ml, and the difference between the two amounting to 0.2±6.3 ml. The two determinations also correlated significntly with a slope of 0.87 (r^2=0.91, p<0.0001). We also determined Vtg(R) in 20 infants with acute bronchiolitis aged 4-53 wks on the day of admission day of discharge. The results were compared to clinical and radiological scores. Vtg(R) fell by 39±14 ml (16%; p=0.01) and corresponded to significant falls in both scores (p< 0.0001). It is concluded that lung volumes can be accurately determined from orthogonal chest X-rays in both healthy and obstructed infants.

63.4

IN VIVO MEASUREMENT OF RENAL BLOOD FLOW (RBF) WITH DYNAMIC CT. M.D. Bentley*, L.O. Lerman*, E.A. Hoffman, M.J. Fiksen-Olsen*, E.L. Ritman and J.C. Romero. Mayo Medical School, Rochester, MN 55905.

Measurement of RBF in vivo with fast CT is complicated by the tubular retention of filtered contrast medium. The kidneys of 8 anesthetized dogs were scanned with the Dynamic Spatial Reconstructor (DSR), during an aortic bolus of iohexol (1.5-2 cc/kg). To determine RBF, the distribution volume of the bolus (adjusted to account for tubular retention, using residual opacity as an index) was divided by mean transit time. These RBF measurements were compared to those made with an electromagnetic flow probe placed on the renal artery. In 5 kidneys, when RBF (probe) was reduced by 10 ± 3, 30 ± 3, and 48 ± 4% with a snare around the renal artery, RBF determined with the DSR decreased from control values of 2.48 ± 0.44 ml/gm/min to 2.51 ± 0.43 (NS), 1.83 ± 0.27 (p<0.05), and 1.36 ± 0.31 (p<0.05) ml/gm/min, respectively. In the remaining 3 kidneys in which RBF was not experimentally altered, no significant changes in RBF were detected with the DSR. In 7 of the 8 dogs, total RBF determinations with the DSR (Y) were linearly related to those made with the probe (X): Y=0.88X + 14 ml/min (r=0.92). These results indicate that changes in RBF may be effectively measured with fast CT if the distribution volume of the kidney is adjusted for the tubular retention of filtered contrast medium.

IONIC CHANNELS IN SMOOTH MUSCLE

64.1

A SMALL MOLECULAR WEIGHT K CHANNEL mRNA IS REGULATED BY ESTROGEN IN MYOMETRIUM. M.B. Boyle*, M. Pragnell*, and L.K. Kaczmarek* (SPON: R.E. Fellows). Univ. of Iowa, Iowa City, IA 52242 and Yale Univ., New Haven, CT 06510.

The enhancement of myometrial excitability by chronic exposure to estrogens may involve the regulation of K channel mRNA. A very slow voltage-dependent K current is expressed in Xenopus oocytes injected with myometrial RNA from estrogen-treated but not estrogen-deprived rats. Injection of size-fractionated RNA suggested that a small mRNA species, similar in size to the 18S ribosomal RNA, was responsible for the expression of the slow K current. We now report the results of Northern blot analysis with cDNA probes showing sequence homology with either the Shaker K channel clones or a kidney K channel clone. A rat brain cDNA clone (K41) showing homology to Shaker detected uterine mRNA species of about 3 kb. The intensity of the 3 kb bands did not differ substantially between uterine RNA from estrogen-treated and estrogen-deprived rats. In addition, blots were probed with a K channel cDNA clone (pKI27) not homologous to Shaker but representing a small kidney mRNA species identified by Takumi et al (Sci. 242:1042) which gives rise to a slow K current in RNA-injected oocytes. This probe recognized an mRNA species of about 800 bases in estrogen-treated uterine RNA, and this species appeared to be present in much lower amounts in uterine RNA from estrogen-deprived rats. Similar bands were detected in lanes containing kidney and heart RNA. Our results suggest that the mRNA species regulated by estrogen is unrelated to Shaker but may be closely related or identical to the K channel mRNA cloned from kidney.

64.2

K_{Ca} CHANNELS FROM CORONARY SMOOTH MUSCLE, INCORPORATED INTO BILAYERS, ARE BLOCKED BY ANGIOTENSIN II. L. Toro*, M. Amador* and E. Stefani*. (SPON: D. Kunze). Baylor College of Medicine. Houston, TX 77030.

Ca-dependent K channels (K_{Ca}) (260 ± 23 pS; n=6, ± S.D.) from porcine coronary arteries were incorporated into lipid bilayers using a 260/60 KCl gradient. The probability of opening (P_o) at -60 mV was 0.7 and 0.03 at pCa of 4 and 6.5, respectively. K_{Ca} channels were charybdotoxin sensitive (20 nM). Angiotensin II (AngII) (20-150 nM) blocked K_{Ca} channel activity by diminishing the P_o, while the amplitude remained intact. The $K_{1/2}$ of blockade was 40 nM. At -20 mV, 20 nM AngII diminished the P_o from 0.92 to 0.87 (6%), while 100 nM further decreased the P_o to 0.22 (76%). This effect was installed within the first 5 minutes after the addition of AngII to the extracellular side of the channel. The kinetics of the channel was also modified by AngII. In the presence of 100 nM AngII the open time constant (τ_{on}) diminished from 40 to 8 ms; the close time constant (τ_{off}) of 2 ms remained unchanged, while a second component of long closures (τ_{off}=26 ms) became apparent. These experiments were performed with K_{Ca} channels in bilayers where cytoplasmic components are presumably absent, and if present, they are expected to be infinitely diluted in the bathing solution. Thus, it is plausible that AngII blocks K(Ca) channels by directly interacting with a site that modulates their activity and not via second messengers. Also, the results indicate that a mechanism of action of this vasoconstrictor peptide is via the closing of K_{Ca} channels, with a subsequent depolarization of the cell membrane and contraction of smooth muscle. Supported by American Heart Assoc., Texas Affiliate.

64.3

VOLTAGE DEPENDENT CALCIUM CHANNELS, CALCIUM DEPENDENT POTASSIUM CHANNELS AND VOLTAGE DEPENDENT POTASSIUM CHANNELS OF CULTURED HUMAN UTERINE SMOOTH MUSCLE CELLS. Roger C. Young and Nels C. Anderson Jr., Med. Univ. South Carolina, Charleston, S.C. 29425

Human uterine tissue was obtained from pregnant women at the time of Cesarean section delivery. Primary cell culture was performed and electron microscopy was used to demonstrate smooth muscle morphology. Whole-cell patch clamp experiments were performed on cells between the second and sixth pass. Depolarizing pulses more positive than -20 mV induced inward currents that activated rapidly (less than 2 msec) and deactivated on the timescale of 20 to 50 milliseconds. These voltage dependent channels were permeable to calcium and barium and blocked by cobalt. Maximal inward currents occurred in the range of -10 to 0 mV. These channels began showing inactivation at -45 mV with half maximal inactivation at -30 mV. Following the inward calcium currents, large outward potassium currents were expressed. These outward currents could be blocked by barium, but were only partially blocked by TEA+ or cobalt, and were identified as due to both voltage dependent potassium channels and calcium dependent potassium channels.

64.4

MODULATION OF VASCULAR Ca^{2+}-ACTIVATED K^+ CHANNELS BY CROMAKALIM AND GLYBURIDE. C. H. Gelband*, J.R. McCullough*, and C. van Breemen* (SPON: A. Bassett). Univ. of Miami School of Medicine, Miami, FL 33101

Cromakalim (BRL 34915) and pinacidil apparently relax vascular smooth muscle by opening K^+ channels, thus causing hyperpolarization. These effects are reversed by the ATP-dependent K^+ channel blocker glyburide. We have investigated the effects of these drugs at the single channel level using high conductance Ca^{2+}-activated K^+ channels (BK) isolated from rabbit aorta and incorporated into planar lipid bilayers. In 1 μM internal Ca^{2+}, BRL 34915 (0.05-10 μM, applied internally) shifted the open probability (P(open))-voltage relationship dose-dependently in the hyperpolarizing direction by 7 to 15 mV. Glyburide alone (1-20 μM, applied internally), at -40 mV, had no effect on the P(open) of the BK channel (control 0.108, 1 μM 0.105, 10 μM 0.105, 20 μM 0.105, n=2). However at -55 mV, 20 μM glyburide reversed the stimulation of channel activity induced by BRL 34915. BRL 34915 (10 μM) increased P(open) from 0.140 to 0.214; 20 μM glyburide decreased P(open) to 0.140 (n=3). Qualitatively similar results were observed with pinacidil. These results suggest that modulation of the BK channel by K^+ channel activators may contribute to the vasorelaxant actions of these drugs. Supported by NIH HL-40184 and HL-07188.

64.5

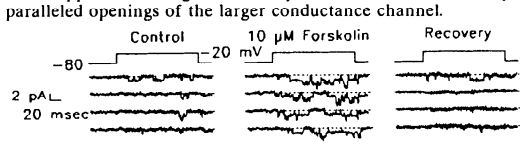
Ca^{2+}- AND VOLTAGE-DEPENDENT INACTIVATION OF CALCIUM CURRENTS IN THE A7r5 SMOOTH MUSCLE-DERIVED CELL LINE. B. Giannattasio*, S. W. Jones*, and A. Scarpa. Dept. Physiology and Biophysics, Case Western Reserve University, Cleveland, OH 44106.

Inactivation of L-type calcium currents in A7r5 cells under whole-cell voltage clamp is faster with Ca^{2+} as the charge carrier than with Ba^{2+}. In Ba^{2+}, inactivation increases monotonically with depolarization. In Ca^{2+}, inactivation parallels the amount of inward current for brief (~60 ms) steps, but a slower inactivation process resembling that in Ba^{2+} also occurs. Lowering Ca^{2+}, but not Ba^{2+}, reduces the amount of fast inactivation. These results suggest the coexistence of two inactivation processes, one fast (τ ~ 20 ms) and Ca^{2+}-dependent, and one slow (τ ~ 200 ms) and voltage dependent. However, strong buffering of intracellular Ca^{2+} did not prevent the Ca^{2+}-dependent component; variability among different cells makes it difficult to evaluate whether Ca^{2+} buffering affected inactivation at all. We studied recovery from inactivation following prepulses designed to produce Ca^{2+}-dependent inactivation (60 ms steps, with Ca^{2+}) or voltage-dependent inactivation (350 ms steps, with Ba^{2+}). Rates for recovery from Ca^{2+}- and voltage-dependent inactivation were similar (~100 ms) at -90 mV, and recovery was slower at more depolarized voltages under both conditions. At -30 mV, recovery from Ca^{2+}-dependent inactivation appeared to be faster than recovery from voltage-dependent inactivation. We propose a three-state cyclic model for "voltage-dependent" inactivation where only transitions to and from the closed state depend on voltage. Binding of Ca^{2+} to either the open or the inactivated state can induce a different inactivated state. (Supported by NIH grant HL 41206.)

64.6

SINGLE CALCIUM CHANNELS IN THE A7R5 CELL LINE. T.N. Marks*, G.R. Dubyak*, and S.W. Jones* (SPON: U. Hopfer). Dept. of Physiol. and Biophysics. Case Western Reserve University. Cleveland, OH. 44106

We have studied properties of single Ca^{2+} channels in the A7r5 cell line derived from rat vascular smooth muscle using the cell attached configuration of the patch clamp technique. Slope conductance of the primary component was ~20 pS between -40 and 0 mV with 90 mM Ba^{2+} in the pipette. Open time was greatly increased in the presence of BAY K 8644 (1 μM) and nifedipine (1 μM) resulted in a reversible suppression of currents. The probability of the channel being in the open state depended on voltage in a sigmoid fashion with an apparent half maximum voltage of ~-10 mV. The probability of being open at 0 mV varied widely between channels (0.2 - 0.9 at 0 mV with BAY K 8644). Addition of 10 μM forskolin to the bath resulted in a reversible increase in the probability of channel opening in most patches, similar to its effect in cardiac myocytes. A smaller conductance channel (~10 pS) was also observed in many patches. In some cases this component had little apparent voltage sensitivity, whereas in others, openings paralleled openings of the larger conductance channel.



64.7

EFFECTS OF ADRENERGIC AND CHOLINERGIC AGONISTS UPON CALCIUM CURRENTS IN INTESTINAL SMOOTH MUSCLE CELLS. Philip I. Aaronson* and Scott N. Russell*. (SPON: Allan W. Jones) St. George's Hospital, London SW 17 ORE, U.K.

Smooth muscle cells were isolated from longitudinal muscle of rabbit small intestine using collagenase and papain. Calcium (Ca) currents were measured with the whole cell patch clamp technique, using cesium-filled pipettes containing 10 mM EGTA, extracellular solutions containing 1.5 mM Ca or barium (Ba), and a holding potential of -60 mV. Peak Ca current amplitude was 200-500 pA with depolarization to 0 mV. Ca current amplitude and current-voltage relationship was not altered by the α-agonist phenylephrine or by the β-agonist isopreterenol (1.0 μM). In contrast, the muscarinic agonist carbachol (CCH, 0.1 - 10 μM) reversibly reduced the amplitude of the Ca current over a period of 2 min without shifting its current-voltage relationship. 1 μM CCH inhibited the current by 27 ± 6 % (mean ± S.E.M., n = 7) when Ca was the charge carrier. This effect was blocked by the muscarinic antagonist atropine (0.1 μM). The effect of CCH was further tested in the presence of ryanodine (1 or 10 μM extracellular, 10 or 100 μM intracellular) with Ba as the charge carrier, to minimize possible Ca-induced inactivation of the current. Under these conditions, 1 μM carbachol irreversibly inhibited the current by 19 ± 3 % (n = 6). These results suggest that activation of muscarinic receptors directly inhibits Ca channels in these cells.

64.8

THREE OUTWARD AND ONE INWARD CURRENT IN SINGLE CELLS FROM GUINEA-PIG PULMONARY ARTERY. R.M.Gow* and R.J.Lang.* (SPON:Hugh O'Brodovich) Department of Physiology, Monash University, Clayton,Victoria, Australia 3168 and The Department of Cardiology, The Hospital for Sick Children, Toronto, Canada.

Pharmacologic and voltage clamp techniques were used to separate the inward and outward currents of single smooth muscle cells from guinea-pig main pulmonary artery (PA). Cells were dispersed enzymatically in saline solution containing collagenase (0.06 gm/ml) and elastase (1.25 U/ml). Whole cell recordings were made at room temperature using low resistance patch pipettes. Current injection evoked electrotonic potentials which showed outward rectification at potentials above -40 mV. Threshold for outward currents elicited by depolarizations under voltage clamp was -40mV also. A calcium activated K current (I_{KCa}) was demonstated by a reduction in the outward current when external Ca was replaced by cobalt or cadmium. Addition of 3mM 4-aminopyridine further reduced the peak outward current and depolarizing steps revealed a current which developed slowly, was sensitive to TEA and did not inactivate (I_K or delayed rectifier). A transient, inactivating outward current (I_A) was identified by subtraction of the delayed rectifier from the control current. Internal and external cesium inhibited the outward currents and a small inward current was observed which increased in the presence of barium, and was blocked by cadmium. In conclusion, the voltage activated outward current in PA cells has 3 components- I_{KCa}, I_K, I_A. A small, voltage activated inward (Ca) current is also present.

65.1

YTTERBIUM-DIETHYLENETRIAMINE PENTAACETIC ACID (Yb-DTPA): A NOVEL CONTRAST AGENT IN MAGNETIC RESONANCE IMAGING (MRI) OF THE KIDNEY. L.B. Kinter, R.E. Rycyna, R.E. Lenkinski[1] and S.K. Sarkar Smith Kline & French Labs., King of Prussia, PA 19406 and University of Pennsylvania[1], Phila., PA 19101

Paramagnetic agents (e.g. Gd-DTPA) are used to increase image contrast by altering relaxation properties of water protons in MRI studies. These agents change the relaxation behavior of protons through dipole-dipole interactions between the spin of unpaired electrons of the paramagnetic metal ions and nuclear spin of protons. Recently it was reported (Magn. Reson. Med. 6, 164, 1988) that contrast generated with Gd-DTPA also arises from the differences in susceptibility between the capillaries containing the contrast agent and the surrounding tissue. In order to separate effects due to T_1 relaxation and susceptibility differences, we chose a lanthanide, Yb-DTPA, which has negligible T_1 relaxivity but has substantial molar susceptibility. We have studied the effects of Yb-DTPA on rat kidney images and find that susceptibility-induced spin dephasing is responsible for the signal intensity decrease observed in T_2-weighted images. Yb-DTPA enhanced the relaxation rate of both the cortex and medulla with the latter being more affected. We conclude that Yb-DTPA is a potentially useful contrast agent for renal MRI evaluations.

65.2

HYPERAMMONEMIA IN RATS STUDIED BY COMBINED ^{15}N AND ^{31}P NMR SPECTROSCOPY

Neil Farrow*, Keiko Kanamori†, Luisa Raiman‡ and Brian Ross* (SPON: Richard J. Bing). *Huntington Med. Res. Insts., Pasadena, CA 91105/Calif. Inst. of Tech., Pasadena, CA 91125; †Univ. of Calif. at L. A., Los Angeles, CA 90024; ‡Univ. of S. Calif., Los Angeles, CA 90033.

In hepatic encephalopathy (HE), ^1H NMR of brain in animals and in man shows accumulation of glutamate/glutamine. The two cannot be distinguished in ^1H NMR. This study explores the use of ^{15}N to resolve the major cerebral metabolite in HE. 1000 μmoles ^{15}N ammonia (A) were given i-v to 24-hour fasted rats over 30 mins. Freeze-clamped liver, kidney and brain were subjected to ^{15}N NMR enzymatic analysis to determine specific activities (SA). *In vivo* ^{31}P NMR and ^1H imaging were performed on a GE 4.7 Tesla CSI spectrometer. Toxic effects of A, with convulsions, were accompanied by a ten-fold increase in blood A. Gamma N of glutamine of SA 100%, was the major cerebral metabolite, with less than 10% label in alpha N of glutamine or glutamate. Hepatic and renal metabolites followed expected labelling patterns, and ^{31}P NMR analysis of extracts or *in vivo* showed full oxygenation. Conclusion: The major N metabolite of brain in hyperammonemia is glutamine, not glutamate.

65.3

EFFECTS OF PRESERVATION SOLUTIONS ON THE RESTORATION OF ENERGY IN THE ISOLATED PERFUSED RAT LIVER AFTER COLD ISCHEMIA: A 31-P MRS STUDY. E.M. Stephens*, S.B. Edge* and R.C. Pace* (SPON: R.M. Berne). Univ. of Virginia, Dept. of Surgery, Charlottesville, VA 22908.

Livers from fasting Sprague-Dawley rats were cannulated and flushed in situ with a preservation solution: Euro-Collins solution (EC), widely used clinically for liver transplant preservation, or the lactobionate solution recently developed at the University of Wisconsin (UW). After excision, the livers were stored at 4 C for up to 14 hours.

After the ischemic period, livers were flushed with Kreb's bicarbonate buffer (pH 7.4). During reperfusion (37C, 30 ml/min, O2 sat. Kreb's bufffer, 10% bovine RBC), 31-P spectra of the liver were recorded (81 MHz, 2 cm. surface coil).

Following 14 hrs of ischemia, baseline levels of ATP (as defined by <10 min. preservation) were restored in the UW-preserved livers within 15 minutes of reperfusion, and moderate concentrations of monophosphates were maintained. Baseline ATP levels were not restored in the EC livers and the mono- and di-phosphate pools were depleted from the low levels observed at the onset of reperfusion. Partial support: Siemens Medical Systems

POSITRON EMISSION TOMOGRAPHY

66.1

INTRATHORACIC LOCALISATION AND QUANTITATION OF TISSUE CARBONIC ANHYDRASE IN DOGS STUDIED WITH PET. E.R.Swenson, C.G. Rhodes,* L.Araujo,* V.Pike,* D. le Bars,* R.M. Effros and J.M.B. Hughes. Dept. Med., Royal Postgrad. Med. Sch. and M.R.C. Cyclotron Unit, Hammersmith Hospital, London W12 ONN, U.K.

^{11}C-acetazolamide (^{11}C-A) was prepared (le Bars et al. J. Appl. Radiol. Isot. 39: 671, 1988) in high specific activity (8 μg in 148 MBq) and injected i.v. into anesthetized dogs (n = 2) in L. lateral decubitus position. Blood was sampled from catheters in pulmonary artery and aorta at 1-2 min. intervals and ^{11}C counts measured in whole blood and plasma. Thoracic PET scans (model ECAT V: CT and I, Knoxsville) were obtained at 2-3 min intervals (15 transaxial planes 7mm thick) with a spatial resolution of 8-10 mm. After 25 min, 20 mg unlabelled A (200 mg given at 37 min) was injected to measure non-specific tissue uptake. Blood volume (for subtraction of vascular ^{11}C-A) was measured after inhalation of $C^{15}O$; tissue density was assessed with a transmission scan (C.G. Rhodes et al. J. Comput. Ass. Tomogr. 5: 783, 1981). Tissue-plasma ratios at equilibrium (MBq ^{11}C-A g^{-1} tissue per ml plasma)were 8.3 (lung), 6.0 (myocardium) and 4.25 (red cells); after displacement the ratios were 1.3, 0.8 and 2.4 respectively. With high specific activity, equilibrium tissue-plasma ratios reflect the Bmax/K_D ratio, the value of 8.5 (lung) matching closely estimates by different methods in rabbit lungs (R.M. Effros et al. J. Appl. Physiol. 49: 589, 1988).

66.2

NEUTROPHIL METABOLIC ACTIVITY IN LOCALISED PULMONARY INFLAMMATION MEASURED NON-INVASIVELY BY POSITRON-EMISSION TOMOGRAPHY (PET). C. Haslett, R.J. Clark, H.A. Jones, T. Krausz and C.G. Rhodes. Royal Postgrad. Med. School and MRC Cyclotron Unit, Hammersmith Hospital, London W12 OHS. UK.

At intervals after direct instillation of strep. pneumoniae or bleomycin into the right upper lobe of rabbits, a transmission PET scan was obtained. This was followed by accumulation of radioactivity detected during 6 consecutive 15 min. periods after i.v. injection of ^{18}Fluorodeoxy glucose (^{18}FDG). Metabolic activity was calculated as the slope of the right (challenged)/left (control) lung ^{18}FDG counts. In apical regions of interest with no challenge, the slope was 1.21 +0.28 (n = 6, min^{-1}* 1000). In response to strep the slope was 1.85 ±0.38 (n = 6) at 4 hr. rising to 12.7 ± 2.33 (n = 8) at 15 hr. and falling to 4.5 ±1.5 (n = 4) at 87 hr. and 0.62 ±0.15 (n = 4) at 230 hr. In contrast, the metabolic response to bleomycin remained elevated; 4.54 ±0.93 (n = 4) at 15 hr., 3.27 ±1.73 (n = 3) at 60 hr., 3.43 ±2.05 (n = 3) at 183 hr., 2.4 ±0.84 (n = 5) at 350 hr., falling back to control levels at 690 hr. In autoradiographs using 3H-FDG in a rabbit 15 hours after strep. and another 14 days after bleomycin, radioactivity was detected only in association with neutrophils. Thus, metabolic activity was localised to neutrophils in 2 models of lung inflammation, with possible implications for monitoring human inflammatory lung disease.

66.3

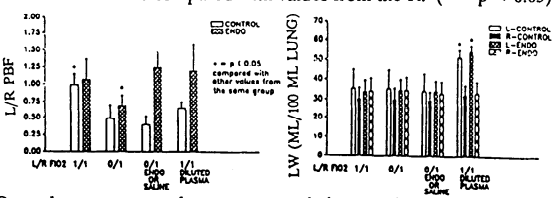
MECHANISM OF VASCULAR DERECRUITMENT DURING ACUTE LUNG INJURY. D.P. Schuster and J. Haller*. Washington University Medical Center, St. Louis, MO. 63110

Interactions between regional pulmonary blood flow (rPBF) and lung water concentration (rLWC) were studied with positron emission tomography (PET) after canine oleic acid (OA)-induced acute lung injury. In 11 supine dogs, rLWC and rPBF correlated strongly with thermal-green dye indicator dilution measurements of extravascular lung water (R^2 = 97%) and thermodilution cardiac output (R^2 = 44%). Changes in LWC correlated with the pulmonary wedge pressure and PET measurements of protein leak (as an index of injury) when considered together (R^2 = 73%), but not with either variable alone. Progressive vascular derecruitment occurred in edematous lung regions after OA in only 6/11 control dogs. In contrast, vascular derecruitment after OA always occurred in 5 other animals given meclofenamate (40% reduction compared with baseline values ($P < 0.05$)). In 21 other dogs, vasodilators (nitroprusside or prostacyclin) did not reverse PBF changes after OA, but did prevent additional derecruitment until the drug infusion was stopped. Regional PBF after stopping the vasodilator infusion was similar in distribution to that in control animals at the same time. We conclude that vessels in edematous lung regions remain vasoreactive until derecruited. Derecruitment itself involves an interaction between edema accumulation and vasoconstriction. Whether derecruitment occurs at all in an individual dog depends on the balance between mechanisms responsible for vascular derecruitment, and vasodilation from prostacyclin.

66.4

ENDOTOXIN BLOCKS VASCULAR DERECRUITMENT IN PULMONARY EDEMA. M. Velazquez, D.P. Schuster, Washington Univ. Med. School, St. Louis, MO.

We used positron emission tomography to sequentially measure regional pulmonary blood flow (PBF) and lung water (LW) in 7 mechanically ventilated dogs before and after left caudal lobe (L) hypoxia, after L hypoxia plus an IV infusion of either 3cc of saline (CONTROL group,n=3) or a bolus of endotoxin (ENDO) (15 mcg/kg), an agent known to block hypoxic vasoconstriction, (ENDO group,n=4) and after instillation of 3 ml/kg hypotonic plasma (1:1 dilution in saline) into a L bronchus. Interstitial and alveolar edema of L was confirmed histologically. Data presented below are mean ± SD. PBF values are expressed as L to right caudal lobe (R) ratio. LW values from L were compared with values from the R. (* = $p < 0.05$)



Our data suggest that vasoconstriction and not mechanical compression is important for vascular derecruitment during interstitial and alveolar edema. Inability to derecruit may be a contributory factor to impaired oxygenation in patients with sepsis and pulmonary edema.

CELL BIOLOGY

67.1

FEATURE ANALYSIS OF PHASE CONTRAST IMAGES OF NEWT EOSINOPHIL CHEMOTAXIS.
S. Gilbert*, L. Lifschitz*, and Fredric S. Fay. Dept. of Physiology, U.Mass. Medical Ctr., Worcester, MA 01655.

Responses of many cells to physiological stimuli involve complex structural changes which in turn reflect local changes in chemistry. While fluorescent probes are now available for measuring changes in molecular distribution in living cells, tools for quantifying structural changes are less well developed. Pattern recognition approaches have been applied to microscopic images to quantitate local structural images underlying polarization and locomotion in newt eosinophils. The cell's outline was found with an interactive edge-detection/connection algorithm and used to calculate its "polarization index" and the location of its centroid. The velocity and direction of motion of the centroid were determined in time sequences of spontaneous locomotion and in response to transient application of chemoattractants and agents that affect the cytoskeleton. Based on textural information in the images, lamellipodia were distinguished from the main cell body of and their formation and fate related to changes in cell shape, speed and direction. Automated processing of large amounts of data provided clear distinctions between spontaneous behavior and responses to experimental intervention and objective tests of hypotheses, formed on viewing time-lapse movies of cell behavior.

67.2

SIMULTANEOUS MEASUREMENT OF CELL MORPHOLOGY AND THE DISTRIBUTION OF INTRACELLULAR [CA++] IN NEWT EOSINOPHILS UNDERGOING CHEMOTAXIS. Rodney A. Brundage* and Fredric S. Fay, Department of Physiology, University of Massachusetts Medical School, Worcester, Mass. 01655

Eosinophils, isolated from the Newt *Taricha granulosa*, were used to assess the relationship between cell morphology and the distribution of intracellular [Ca++] during cell polarization and chemotaxis. These large (60um), rapidly moving (20um/min) cells quickly polarize in response to the application of a heat labile, trypsin sensitive factor(s) in Newt serum. Image analysis software has been developed, to determine a cells boundary, level of polarity, the speed of motion of the geometric centroid, and the direction of its movement from time-lapse video image records. Addition of 5mM EGTA, 10mM Cobalt Chloride, 7uM Ionomycin, or 50uM Verapamil to the bath inhibited cell polarization and chemotaxis to 10% Newt serum. Results using the [Ca++] sensitive fluorescent probe, Fura-II, indicate that intracellular [Ca++] is significantly higher and more heterogenously distributed in polarized cells than in unpolarized cells. A modified epifluorescence microscope will be used to obtain both phase and fluorescence images of chemotaxing, Fura-II loaded eosinophils. Simultaneous examination of changes in cell morphology and the distribution of intracellular [Ca++] during treatment with agents which interfere with Ca++ homeostasis promises to further define the role of [Ca++] in this process. SUPPORT:NIH-HL14523 and NIH-CA39240.

67.3

HIGH SPONTANEOUS & IgE MEDIATED HISTAMINE RELEASE FROM BASOPHILS IN ATOPIC SUBJECTS. J.W. Townley, M. Hiratani, R.G. Townley. Creighton University, Omaha, NE 68178

The purpose of our study was to show functionally different basophilic populations in atopic subjects. We studied the spontaneous histamine release (SHR) & anti IgE induced histamine release (HR) of basophils obtained by density gradient centrifugation on monolayers of Percoll solution, specific gravity (SG) 1.071 (Fr I), SG 1.077 (Fr II), and SG 1.085 (Fr III) in normal and atopic subjects. The leukocyte rich fraction obtained by Dextran EDTA sedimentation was layered on varying densities of Percoll gradient. Cells at the interface between Tris A buffer and Percoll were collected and washed, as was the cell pellet SG 1.071 (Fr IV). The leukocyte suspensions obtained by suspension of each fraction was incubated in Tris ACM with and without anti IgE for 60 minutes at 37 C. Histamine was assayed by double isotopic enzyme assay. The SHR of FRI was higher than that of D.D. (p 0.02). The HR by anti IgE of Fr I was higher than that of D.D. (p 0.05) and Fr IV (p 0.02). The results of Fr II and Fr III were not significantly different with those of Fr I. This data suggests that the releaseability of basophils obtained by Percoll gradient was increased compared to basophils obtained by Dextran-EDTA alone. This data also suggests the existence of functionally different basophil populations in atopic subjects.

67.4

DIPYRIDAMOLE INHIBITION OF HCO_3^-/Cl^- EXCHANGE IN HUMAN ERYTHROCYTES. C.G. Vanoye*, T.A. Heming & A. Bidani, Dept. Medicine, Univ. Texas Medical Branch, Galveston, TX 77570.

Dipyridamole, an antiplatelet agent used in treatment of arteriothrombotic disorders, has been postulated to affect Band 3-mediated erythrocyte anion exchange. We have quantitated the effects of dipyridamole on HCO_3^-/Cl^- exchange in human red cells at 37°C. HCO_3^-/Cl^- exchange was monitored by following changes in extracellular pH (pH_o) when an acidic phosphate buffer solution (pH_o 6.7) was mixed with a red cell suspension (pH_o 7.2) containing HCO_3^- (4.4-8.8 mM) in a stop-flow rapid reaction apparatus. In the presence of exogenous carbonic anhydrase, membrane translocation of HCO_3^- for Cl^- is the rate-limiting step for H^+ equilibration across the cell membrane. Net efflux of HCO_3^-(nmol/cm^2 sec) across the red cell membrane and apparent permeability of red cells to HCO_3^- (cm/sec) were calculated from the initial $\Delta pH_o/\Delta time$, hematocrit and extracellular buffering capacity. Dipyridamole was found to be a potent inhibitor of red cell HCO_3^-/Cl^- exchange, with an I_{50}~1 μM. A Dixon plot of HCO_3^- efflux rate versus dipyridamole concentration yielded a mixed competitive-noncompetitive inhibition with a K_I~0.3 μM at 37°C. These results suggest that low concentrations of dipyridamole can significantly inhibit erythrocyte HCO_3^-/Cl^- exchange. High dose regimes of dipyridamole, such as used for thallium scintigraphy, may adversely affect the kinetics of capillary CO_2 exchange in vivo.

67.5

IODOACETATE ACTION ON FLUID-PHASE ENDOCYTOSIS IN OK CELLS. SA Kempson, KJ Kunkler* and H Murer*. Indiana University, Indianapolis, IN, and University of Zurich, Switzerland.

Fluid-phase endocytosis in renal epithelial OK cells was measured by cell uptake of horseradish peroxidase (HRP), lucifer yellow (LY) and ^{14}C-sucrose (S). Iodoacetate, inhibitor of glycolysis, and cyanide, inhibitor of mitochondrial respiration, were used to determine if uptake was dependent on a metabolic energy supply. Incubation of OK cells with 1 mM iodoacetate or 5 mM cyanide for 1 h decreased cell ATP content by 72% or 62%, respectively. Iodoacetate decreased HRP uptake by 42 ± 5% but LY uptake was increased by 286 ± 64% (n=3). S uptake also was increased by iodoacetate. In contrast, both HRP and LY uptake were inhibited significantly by cyanide. Iodoacetate reduced the intracellular K^+/Na^+ ratio from 9.20 (controls) to 0.34, but in cyanide treated cells the ratio was 10.1 (n=5). Total Pi uptake (Na^+ present) was not altered by iodoacetate but there was a 30-fold increase in the Na^+-independent Pi uptake. Cyanide affected neither total Pi uptake nor the Na^+-independent Pi uptake. We conclude that iodoacetate, in addition to inhibiting glycolysis, alters plasma membrane permeability to ions and small molecules such as LY and S. This may be due, in part, to alkylation of -SH groups of membrane proteins. These non-specific effects limit the usefulness of iodoacetate for determining the energy-dependence of fluid-phase endocytosis in OK cells.
(Supported by NIH and Swiss National Fond).

67.6

GAP JUNCTIONS BETWEEN ENDOTHELIAL CELLS: UNITARY CONDUCTANCE, IDENTITY OF THE CHANNEL PROTEIN, AND RESPONSE TO SECOND MESSENGERS AND TRYPANOSOME INFECTION. D.C.Spray, A.Moreno*, C. Roy, J.Saez, J.M.Burt, E.Hertzberg, A.Campos de Carvalho, R. Dermietzel, Y.Hatcher, M.Wittner, & H.Tanowitz. Einstein Coll. Med., Bronx, NY.

Morphological and physiological properties of gap junctions between human umbilical vein endothelial cells (HUEC) have been followed in primary culture. In freeze fracture of confluent cultures, junctions are quite small. Dye coupling is density dependent, with coupling markedly higher at margins of wounds and at low cell density. Tumor promoting phorbol esters and diacylglycerol reduce dye coupling within tens of min. In response to 8 Br-cAMP, junctional conductance (g_j) in voltage clamped cell pairs rapidly increases if extracellular Ca is absent (no added Ca, 1 mM EGTA); g_j is rapidly reduced by 8 Br-cAMP in high Ca. Immunocytology with antibodies specific for sequences of connexin 43, the heart gap junction protein, indicate that this protein is a component of HUEC gap junctions. Single channel studies, under conditions where g_j is rendered reversibly low by treatment with the volatile anesthetic halothane, reveals unitary conductances for these channels of about 90 pS with 140 mM CsCl in the patch pipette and about 50-60 pS when the pipettes contain 110 mM KGlutamate. This unitary conductance is similar to that obtained on pairs of neonatal cardiac myocytes from rat, a preparation in which the junctional protein is connexin 43. We conclude that HUEC gap junctions are comparable in unitary conductance, responsiveness to cAMP and contain the same connexin as cardiac gap junctions. HUEC and cardiac myocytes responded similarly to infection with the trypanosome *T. cruzi*, which led to disappearance of dye coupling and organized junctional complexes.

67.7

PUTATIVE ROLE OF PROTEIN IN EMBRYO CULTURE MEDIA. Barbara A. Shirley and Larry P. Flood*. Univ. of Tulsa, Tulsa, OK 74104

This study tested the hypothesis that one role of protein in embryo culture media is to protect embryos against potentially embryotoxic substances in the media. Mouse embryos were cultured in modified Krebs Ringer bicarbonate medium and in modified Tyrode's medium, aliquots of which were supplemented with 4 g/l of the protein bovine serum albumin (BSA) while other aliquots were left protein-free. The media were prepared using water samples that differed in purity, as reflected by differences in conductivity, with tap water being least pure (and considered to have the greatest potential for being embryotoxic) and water that had been purified by reverse osmosis, Milli-Q filtration, and triple distillation being most pure. Embryos were placed in the media while in the two-cell stage of development and their development was assessed after 24, 48, and 72 hours of culture. Rate of embryo development in BSA-supplemented media was greater than that in protein-free media only when the media were prepared with the least purified water samples. Because these water samples would have contained substances not contained in media prepared with purer water, or would have contained the substances in higher concentrations, the data supported the hypothesis that protein can protect embryos during culture by negating effects of embryotoxic substances in the media. (Supported by a grant from the Hillcrest Infertility Center, Tulsa.)

67.8

SPONTANEOUS CONTRACTIONS AND CHRONOTROPIC RESPONSES OF CULTURED MOUSE MYOCARDIAL CELLS INFECTED WITH TRYPANOSOMA CRUZI. Octavio Aprigliano, Masako Masuda* and Maria de Nazareth Meirelles* Inst. de Biofisica Carlos Chagas Fº, UFRJ, and Dept. de Ultraestrutura e Biologia Celular, FIOCRUZ, Rio de Janeiro, Brasil

The frequency of spontaneous contractions (FSC) and the responses to norepinephrine (NE) were studied in heart cell cultures 2 days after in vitro infection with T.cruzi. Single cells or clusters were suffused with physiological saline solution and visually monitored before and during exposure to NE. The FSC increased with the NE concentration, and this effect could be blocked by phentolamine. Compared to controls, infected cells showed a higher FSC (23%), and were less sensitive to NE. Since the parasites are internalized by these cells, which are not professional phagocytes, phagocytosis "per se" could explain the data. However, cells made to internalize ferritin particles and cultures kept in conditioned medium did not show any of the changes observed in the infected cells. We conclude that the results obtained are attributable to the intracellular presence of the parasite, making this an experimental model for studies of T.cruzi-myocardial cell interaction. Supported by Grants from UNDP/World Bank/WHO, FINEP, CNPq and CEPG-UFRJ.

67.9

ROTATION OF PLASMA MEMBRANE PROTEINS MEASURED BY POLARIZED FLUORESCENCE DEPLETION. D.A. Roess, N.A. Rahman*, and B.G. Barisas*, Colorado State Univ., Ft. Collins, CO 80523

We have implemented a new laser microscopic method, polarized fluorescence depletion (PFD), for measuring the rotational dynamics of functional membrane proteins on individual, microscopically selected cells under physiological conditions. As examples, the rotational correlation time of Fc_ϵ receptors ($Fc_\epsilon R$) on the surface of 2H3 rat basophilic leukemia cells is 79.9 ± 4.4 μsec 4°C when labeled with eosin conjugates of IgE. This value is consistent with the known 100 kDa receptor size. When labeled with intact F4 anti-$Fc_\epsilon R$ antibody, the rotational correlation time for $Fc_\epsilon R$ is increased about 2-fold to 170.8 ± 6.5 μsec, consistent with receptor dimer formation on the plasma membrane and with the ability of this antibody to form $Fc_\epsilon R$ dimers in solution. We have also examined the rotational diffusion of the luteinizing hormone receptor (LHR) on plasma membranes of small ovine luteal cells. LHR, when occupied by ovine luteinizing hormone (oLH), has a rotational correlation time of 20.5 ± 0.1 μs at 4°C. When occupied by human chorionic gonadotropin (hCG), LHR have a rotational correlation time of 46.2 ± 0.4 μs suggesting that binding of hCG triggers additional LHR interactions with plasma membrane proteins. Together these studies suggest the utility of PFD measurements in assessing molecular size and molecular associations of membrane proteins on individual cells. Supported by NIH grants HD-23236 (DAR) and AI-21873 and AI-26621 (BGB).

68.1

LOCAL CEREBRAL BLOOD FLOW DURING BEHAVIORAL STATE TRANSITIONS IN FETAL SHEEP. R.M. Abrams, K.J. Gerhardt* and D.J. Burchfield*. Depts. OB/GYN, Speech and Pediatrics, Univ. of Florida, Gainesville, FL 32610

Local cerebral blood flow (LCBF) in 3 near-term fetal sheep was measured during 10 transitions from non-rapid eye movement sleep (NREM) to REM and 14 transitions from REM to NREM. Changes in LCBF were measured continuously by chronically implanted cortical and subcortical thermojunctions (TJs), one heated 1-2°C above a reference TJ placed contralaterally in the brain. Behaviorial states were assessed by visual analysis of strip chart recordings of ECoG, EOG and neck EMG electrical activity. The frequency contents of the ECoG were later measured from an FM taped signal beginning 3 min prior to and ending 3 min after the transition in behavioral state. Electrical activity in 2 frequency bands (.8-1.1 Hz and 17.8-22.4 Hz) was measured during twelve 30 sec epochs and expressed in dB. LCBF rise was evident by 12 sec after transition from NREM to REM and reached an asymptote by 72 sec. The spectral energy in the low frequency band declined (8 dB) by 90 sec after the transition from NREM to REM while spectral energy in the high frequency band increased only slightly. LCBF fell and low frequency energy rose by 8 dB after transitions from REM to NREM. Spectral energy in the high frequency band decreased slightly.
Supported in part by NIH Grant HD-20084.

68.2

FACILITORY EFFECTS OF CALCIUM CHANNEL BLOCKING AGENTS ON PROTECTION BY DIPHENYLHYDANTOIN AGAINST MAXIMAL ELECTRIC SHOCK INDUCED SEIZURES IN MICE. Mary I. Leadbetter* and S.S. Parmar. University of North Dakota School of Medicine, Grand Forks, ND 58202 and Alfred I. duPont Inst., Wilmington, DE 19899.

Calcium channel entry blocking agents have been shown to exhibit anticonvulsant properties. CF-1 male albino mice, 25-35 gms, were pretreated with diltiazem (40 mg/kg, i.p.), verapamil (80 mg/kg, i.p) and nifedipine (10 mg/kg, i.p.) for one hour, then challenged with maximal electric shock (MES) (70 mA, 0.2 sec., 100 pulse/sec.). Diltiazem and verapamil provided no protection from MES-induced convulsion as compared to vehicle treated controls, whereas nifedipine provided 28% protection. The ED_{50} of phenytoin was determined to be 4.8 mg/kg, i.p. Pretreatment with the calcium channel antagonists diltiazem and nifedipine, as previously described, potentiated the anticonvulsant activity of phenytoin from 50% to 90% and 80% respectively. Pretreatment with verapamil provided no increase in protection. These results suggest a role for calcium channel entry blockers in the treatment of seizure disorder. Further, the protective effect of diltiazem and nifedipine is synergistic with the anticonvulsant phenytoin.
(Supported in part by the Bush Foundation Developmental Grant, Max Baer Heart Grant and the Patricia Roberts Harris Fellowship.)

68.3

INHIBITION OF VOLTAGE-GATED Ca^{2+} CHANNELS IN SMALL CELL LUNG CARCINOMA BY M_3 MUSCARINIC ACETYLCHOLINE RECEPTOR ACTIVATION. Carol L. Williams* and Vanda A. Lennon* (SPON: Joseph H. Szurszewski). Mayo Clinic, Rochester, MN 55905.

Small cell carcinoma of the lung (SCC) expresses several neuronal characteristics, including voltage-gated Ca^{2+} channels (VGCC). It also expresses muscarinic acetylcholine receptors (mAChR). In testing the possibility that VGCC may be functionally coupled to mAChR in SCC cell lines, we found that depolarization-dependent Ca^{2+} influx was inhibited by carbachol (IC_{50} = 0.78 μM) and oxotremorine (IC_{50} = 0.69 μM). Equilibrium dissociation constants for several mAChR antagonists indicated that a mAChR of M_3 subtype was involved. Inhibition of depolarization-dependent Ca^{2+} influx did not correlate with the rapid rise in cytosolic free Ca^{2+} concentration that was induced by carbachol, but did correlate with the accumulation of inositol trisphosphates (IP3). Phorbol 12-myristate 13-acetate, a protein kinase C (PKC) activator, abrogated rather than enhanced the carbachol-induced IP3 generation and inhibition of Ca^{2+} influx. The inactive compound 4α-phorbol had no effect. These data suggest that IP3, rather than PKC, mediates the inhibition of VGCC caused by carbachol. SCC cell lines provide a novel human model for studying the neuronal phenomenon of mAChR-mediated inhibition of VGCC activity.
Supported by grant CA-37343 from the National Cancer Institute.

68.4

CHARACTERISTICS OF THE POTENTIATION OF INHIBITORY JUNCTION POTENTIALS OF GUINEA-PIG ILEUM BY CALCIUM CHANNEL ANTAGONISTS. G.M. Lees*, D.J. Leishman*, A.H. Macleod* and B.J.A. Mankelow* (SPON: J.H. Szurszewski). University of Aberdeen, Aberdeen, AB9 1AS, Scotland, U.K.

Non-adrenergic, non-cholinergic inhibitory junction potentials (IJPs) were recorded intracellularly from circular muscle of guinea-pig isolated ileum in response to single pulses or a volley of transmural stimuli. IJP amplitude (corrected for non-linear summation) was related linearly to $[Ca^{2+}]_o$ (1.4-4.9 mM) and inversely to $[K^+]_o$ (0.47-47 mM). Apamin (20-250 nM) totally and reversibly abolished the IJP without affecting the resting membrane potential (r.m.p.), whereas the potassium channel activator, cromokalim (100 nM) significantly increased r.m.p. but did not affect the mean amplitude of the IJP. IJPs showed marked potentiation in the presence of the calcium channel antagonist, nifedipine (0.3-3.0 μM), an effect that was independent of $[Ca^{2+}]_o$ and was actually augmented, not attenuated, in the presence of raised $[Ca^{2+}]_o$. Potentiation of IJP was also seen in the presence of Bay K 8644 (3 μM) alone; in combination with nifedipine (3.0 μM), Bay K 8644 caused a further increase in IJP amplitude. These findings suggest that nifedipine did not act as a calcium channel antagonist under these conditions to potentiate the IJP. Adenosine and its agonist analogues, N^6-L-2-phenylisopropyladenosine (R-PIA) and 5^1-N-ethylcarboxamidoadenosine (NECA) (2-5 μM), significantly depressed IJP amplitude without affecting r.m.p. and could reverse the potentiation of IJP induced by nifedipine (0.5 μM). The adenosine A_1-receptor antagonist, 8-phenyltheophylline (5-20 μM) potentiated the IJP; r.m.p. was not affected. It is suggested that the potentiation of the IJP by nifedipine may be due to a blockade of adenosine receptors.

68.5

EFFECTS OF CENTRAL VERSUS SUBCUTANEOUS INFUSION OF BUSPIRONE ON AGGRESSION. M.L. Leavitt, J.C. Maroon*, and T.R.P. Price*. Allegheny-Singer Research Institute, Pittsburgh, PA 15212

The present study investigated the mechanism of buspirone's antiaggressive action by comparing the effects of intraventricular (IVT) vs. subcutaneous (SQ) B infusion on shock-induced attack behavior (SIA). Pairs of male 6-hydroxydopamine-treated rats (IVT, 200μg) had baseline SIA measured before implanting osmotic minipumps that infused either: A. SQ H_2O, B. SQ B (10mg), C. SQ B (20mg), D. SQ B (30mg), E. IVT H_2O, F. IVT B (10mg), or G. IVT B (20mg/kg/day). SIA was subsequently monitored every 2-3 days and averaged for each pre-treatment and treatment-week. SIA was significantly reduced by SQ but not by IVT buspirone infusion.

	N	Baseline	Treatment Week 1	Treatment Week 2
A.	5	33.0±2.2	31.7±1.7	33.1±3.9
B.	7	29.4±2.6	27.0±2.3	26.6±3.0
C.	5	34.3±1.1	26.1±1.2**	27.9±1.9*
D.	7	34.4±2.4	21.4±3.5**	21.6±2.9**
E.	5	35.2±2.2	36.1±1.0	34.7±2.6
F.	4	28.8±0.8	34.0±2.4	36.0±1.8
G.	5	30.1±0.8	27.1±1.2	

*p<.02, **p<.001 vs. baseline

These results indicate that buspirone's antiaggressive effect may not be centrally mediated.

68.6

REFLEX RESPONSES IN RENAL NERVE ACTIVITY AND RENAL BLOOD FLOW TO STATIC MUSCLE CONTRACTION IN ANESTHETIZED CATS. Kanji Matsukawa*, P. Tim Wall, L. Britt Wilson, Jere H. Mitchell. U.T. Southwestern Medical Center, Dallas, TX 75235-9034.

The aim of this study is to directly examine the relationship between changes in renal sympathetic nerve activity and renal blood flow during static muscle contraction. Ten cats were anesthetized with α-chloralose (70 mg/kg, iv). The left kidney was exposed retroperitoneally and recording electrodes for renal sympathetic nerve activity were implanted on a renal nerve branch. Renal blood flow was measured using an ultrasonic doppler flow probe that was placed on the left renal artery. We evoked static muscle contraction by stimulating the L_7 and S_1 ventral roots for 1-5 min (intensity, 3 X motor threshold; frequency, 20-40 Hz). During static muscle contraction, renal sympathetic nerve activity and arterial blood pressure increased 56+11% and 33+6%, respectively. In addition, renal blood flow decreased by 18±2% and renal vascular resistance increased by about 60%. The time courses of the changes in renal sympathetic nerve activity and renal blood flow were quite similar. After renal denervation, renal blood flow did not change during static contraction or passively increased in proportion to an increase in arterial blood pressure. Thus, we conclude that the reflex activation of renal sympathetic nerve activity in response to static muscle contraction induces renal vasoconstriction and decreases renal blood flow.

68.7

CARDIOVASCULAR RESPONSES TO HYPOXIA AND HYPERCAPNIA IN BARODENERVATED CONSCIOUS RATS. Benjimen R. Walker and Barbara L. Brizzee. Dept. of Physiology, University of New Mexico School of Medicine, Albuquerque, NM 87131.

Experiments were performed to examine the role of the arterial baroreceptors in the cardiovascular responses to acute hypoxia and hypercapnia in conscious rats. All animals were chronically instrumented with a pulsed Doppler flow probe on the ascending aorta for cardiac output measurement and with arterial and venous catheters. One group of rats remained intact, whereas a second group was barodenervated by stripping connective tissue and applying 10% phenol in ethanol to the aortic and carotid reflexogenic zones. Only animals demonstrating minimal bradycardic responses to a series of pressor doses of phenylephrine administered 1wk after surgery were used in the barodenervated group. Both groups of animals possessed intact peripheral chemoreceptive function as evidenced by normal ventilatory responses to hypoxia. The cardiovascular responses of conscious, unrestrained rats were monitored during exposure to either hypercapnia (10% CO_2), hypoxia (9.5% O_2) or room air. Hypercapnia resulted in bradycardia and reduced cardiac output in intact rats, however this response was eliminated by barodenervation. Exposure to hypoxia caused a marked fall in blood pressure and total peripheral resistance in barodenervated rats which was not observed in intact animals. It is concluded that the arterial baroreflex is an important component of the overall cardiovascular responses to both hypercapnic and hypoxic stimuli in the rat. Supported by HL42778 and a Grant-in-Aid from the American Heart Association.

68.8

PHENYLEPHRINE MODULATES CARBACHOL-INDUCED BRADYCARDIA THROUGH AN ALPHA-2 RECEPTOR. B.J. Pardini, D.D. Lund, and P.G. Schmid. VA Med Ctr & Dept of Internal Medicine, U of Iowa, Iowa City, IA 52246.

Phenylephrine has been shown to have two different modulatory effects on parasympathetic control of heart rate: 1) inhibition of bradycardia induced by cervical vagus stimulation through alpha-1 adrenergic inhibition of acetylcholine release and 2) facilitation of bradycardia produced by the nicotinic actions of carbachol which presumably causes direct activation of intracardiac ganglion cells. The purpose of the present investigation was to determine if the alpha-2 adrenergic receptor is responsible for facilitation of the carbachol effects. Sprague Dawley rats were anesthetized (urethane, 1.2 g/kg, ip), and instrumented with arterial and venous catheters, and ECG leads. The cervical vagi were sectioned and propranolol (1 mg/kg, iv) was administered. Carbachol (0.5, 1.0, 2.0, and 4.0 µg/kg) was injected to activate intracardiac ganglion cells or the cervical vagus nerve was electrically stimulated (0.5 mA, 0.5 msec, 1, 3, 5, and 10 Hz) during phenylephrine infusion (20 µg/kg•min) with and without the alpha-2 blocker, yohimbine (1 mg/kg). Changes in heart rate were recorded. The carbachol-induced changes in heart rate (beats/min; mean ± SEM; N=9; *=p<0.05 by ANOVA) were:

Carbachol (µg/kg):	0.5	1.0	2.0	4.0
Control	19±5	26±6	40±8	85±9
Phenylephrine	18±2	*43±6	*67±8	*127±14
Phenylephrine + Yohimbine	13±2	25±4	47±7	77±11

Thus, yohimbine antagonized the ability of phenylephrine to facilitate carbachol-induced bradycardia. Furthermore, yohimbine did not detectably affect the ability of phenylephrine to attenuate vagal-induced bradycardia, an alpha-1 mediated effect. These data indicate that potentiation of carbachol's actions on heart rate by phenylephrine is through an alpha-2 adrenergic receptor. (Supported by Vet Admin, NIH HL38137, and AHA - Iowa Affiliate)

68.9

MODEL SIMULATION OF BARORECEPTOR RESETTING. H. Stinnett and D. Ewert. Physiol. Dept., UNDSM, Grand Forks, ND 58202

A linear differential equation model was written to relate sinus wall mechanical properties to those of the baroreceptor. The model utilized elasticity and viscosity coefficients determined experimentally from rabbit carotid sinus wall and baroreceptor responses to single step change in intrasinus pressure. Model development and testing were performed on digital computers. The wall portion of the model consisted of four interactive equations. Baroreceptors were modeled by three different receptor equations; where each equation represented a unique type of baroreceptor. The three receptor equations constituted a set. A set of receptor equations were mathematically associated to two different locations within the wall model. Mechanical events, at receptor-wall junction, were converted to activity using an experimentally determined transduction coefficient. This coefficient was the same for all receptors. To simulate conditions which cause baroreceptor resetting, the model was presented input of 6 one minute step increases and then decreases in force. Responses of receptor activity were plotted relative to force amplitude at each step. Criteria for model receptor resetting was hysteresis of this relationship curve. Hysteresis was found for model receptors which also simulated characteristics of baroreceptor adaptation. Using a ramp force input, other receptors were found to simulate characteristics of varied baroreceptor activation threshold, gain and activity saturation. Part sup. BRSG S07 RR5 407-22.

68.10

HEART RATE (HR) RESPONSES TO THREE TESTS OF THE VAGAL-CARDIAC PATHWAY: VALSALVA MANEUVER (VAL), RESPIRATORY SINUS ARRHYTHMIA (RSA), COLD FACE TEST (CFT; DIVING REFLEX) Martha E. Heath. Dept. of Rehab. Med., Columbia University College of Physicians & Surgeons, NY, NY., 10032

The purpose of this study was to compare the HR responses to tests of the vagal-cardiac pathway and assess their relative value in clinical autonomic assessment. Subjects were 32 healthy men and women 18-45 years old and were supine for all tests. HR was monitored on a beat to beat basis. VAL: 15s, 40 mmHg forced expiration assessed as the difference between minimum (min) and maximum (max) HR. RSA: 6 deep breaths taken in one minute and assessed as the difference between min and max HR for breaths 3-5. CFT: bilateral 60s application of 0°C compresses assessed as the difference between baseline mean and test min HRs. The HR response was largest for VAL and smallest for CFT.

VAL (y-axis) vs RSA (x-axis): $y = 0.874X + 35.848$ ($r = 0.32$)
CFT (y-axis) vs RSA (x-axis): $y = 0.539X + 1.398$ ($r = 0.87$)

This is because the VAL response includes sympathetic mediated tachycardia, and the CFT response is diminished by reductions in baseline HR due to resting vagal tone. Neither of these factors affect RSA which results from inhibition of sympathetic and parasympathetic input to the heart in the early inspiratory phase (Koizumi & Kollai, Neurol. Neurobiol. 31, 153-167, 1987) and vagal suppression of HR beginning late in inspiration and continuing during expiration. It is concluded that RSA provides the best test of vagal-cardiac function and CFT provides a well correlated accessory test that has the advantage of using an alternate afferent pathway (trigeminal). (SPON: Vidda Foundation)

68.11

HALOTHANE SUPPRESSES SYMPATHETIC EFFERENT NERVE ACTIVITY IN RABBIT SPLANCHNIC NERVE. Bruce McCallum*, Zeljko Bosnjak, and John P. Kampine. Medical College of Wisconsin, Milwaukee, WI 53226.

Little information exists on the effect of Halothane (H) on the sympathetic efferent nerve activity (SENA) to the splanchnic bed. This study provides direct evidence for the suppressive effect of H (0.5% and 1.0% vaporizer settings) on the reflex response of the SENA. Bipolar electrodes, composed of two single strand teflon coated stainless steel wires (O.D.=0.25mm) in silastic tubing, were fixed to the splanchnic nerve of 6 chloralose anesthetized rabbits with Wacker Silgel. The nerve was sectioned distal to the celiac ganglion, and efferent activity was verified by Hexamethonium (10mg/kg) administered after the end of the study. Neural activity was amplified 40,000X, passband filtered (.1-2 KHz), and subsequently time averaged over 200ms time increments. Reflex stimulation was accomplished by means of aortic nerve stimulation (ANS, 0.05 mA) and bilateral carotid occlusion (BCO). SENA was expressed as percent of initial baseline. The significant changes in SENA during stimulation (*p<0.05) and significant differences in SENA between initial state and the corresponding state at different H levels (+p<0.05) were as follows:

Halothane	0.0%		0.5%		0.0%		1.0%	
	base	stim.	base	stim.	base	stim.	base	stim.
ANS	100	21*	94	39*	104	28*	70+	53+
BCO	100	125*	93+	96+	98	121*	82+	83+

SENA was significantly reduced during 0.5% and 1.0% H as compared to 0% H. 0.5% and 1.0% H effectively abolished the pressor response during BCO, whereas only 1.0% H significantly diminished the depressor response during ANS.

69.1

UPTAKE OF THE OXIDIZED AND REDUCED FORMS OF ASCORBATE BY THE RABBIT IRIS-CILIARY BODY. Robert S. Noyes* and Richard C. Rose. Department of Physiology, School of Medicine, University of North Dakota, Grand Forks, ND 58202.

Significant evidence exists for a carrier-mediated active transport mechanism for the uptake of ascorbate (AA) into the rabbit ciliary body. This uptake has previously been shown to be saturable, inhibited by ouabain, and dependent upon Na^+, K^+, glucose, and temperature. AA rapidly oxidizes to dehydroascorbic acid (DHAA), even in the presence of thiourea. Therefore, we studied the uptake of AA, DHAA and diketogulonic acid (DKG). We also examined the form of the molecule once it had been taken up into the tissue. Isolated rabbit iris-ciliary bodies were mounted in modified Ussing-Zerahn-type chambers at 37°. The anterior (blood) surface was exposed for 8 min. (a duration of time that avoids excessive degradation of ^{14}C-isotope from AA → DHAA → DKG) to one of the three forms of ^{14}C-isotope. The isotope taken up by the tissue was extracted in 10% meta-H_2PO_4. The chamber solutions and the tissue extract were analyzed by HPLC to determine the form of the ^{14}C-isotope. DHAA was taken up at least as rapidly as AA, but DKG uptake was undetectable. ^{14}C-isotope from either AA or DHAA exposed tissues was found in the tissue as AA. Ouabain-containing solutions inhibited the uptake of both DHAA and AA essentially equally. It appears as though the rabbit iris-ciliary body clears DHAA from the blood, reduces it, and delivers AA to the aqueous humor. NIH support.

69.2

K^+ CAUSES SWELLING OF DARK CELLS FROM THE CRISTA AMPULLARIS WHICH IS Na^+ AND Cl^- DEPENDENT AND INHIBITED BY PIRETANIDE. Philine Wangemann*, Daniel C. Marcus. Boys Town National Institute, Omaha, NE 68131

We measured epithelial cell height in order to monitor cell volume in an unsided preparation of dark cells from the crista ampullaris of the inner ear of the gerbil. At 10 sec intervals, 6 to 15 measurements were made encompassing 2 to 4 cells of a tissue; n = number of tissues. Isotonic elevation of K^+ from 3.6 to 25 mmol/l in a PO_4-buffered, HCO_3-free solution led to swelling from 6.2±0.5 (SE) to a peak of 8.7±0.6 µm (n=10) during the first 30 to 40 sec, which was followed by a regulatory volume decrease. We tested for the ionic requirements of the K^+-evoked swelling process. Swelling was absent in both isotonic Cl^--free solution (gluconate) and isotonic Na^+-free solution (N-methyl-D-glucamine) and was inhibited by the loop diuretic Piretanide (10^{-5} mol/l). In the presence of Piretanide, K^+ caused an increase in cell height of only 0.7±0.1 um, as compared to 2.9±0.4 µm (n=6) under control conditions. Piretanide by itself caused no significant change in cell height, whereas Cl^--free solution and Na^+-free solution each significantly decreased cell height from 6.4±0.8 to 5.6±0.8 µm (n=6) and from 6.7±0.2 to 6.2±0.2 µm (n=4), respectively. The data demonstrate a solute uptake mechanism dependent on K^+, Cl^- and Na^+ which is sensitive to Piretanide, most likely the $Na^+2Cl^-K^+$ cotransporter.

Supported by the Deafness Research Foundation and NIH NS 19490

69.3

DETERMINATION of Na^+-P_i SYMPORTERS IN MICROVILLAR BRUSH BORDER MEMBRANES (BBM). J.-T. Lin*, A. Hoppe*, and T.P. Dousa. Mayo Clinic and Foundation, Rochester, MN 55905

[^{14}C]-Phosphonoformic acid ([^{14}C]-PFA), a specific competitive inhibitor of Na^+-P_i cotransport across epithelial BBM, was used to determine density of Na^+-P_i symporters in BBM from rat renal cortex. Studies were conducted on freshly prepared BBM vesicles (BBMV) and on BBMV extracts solubilized with s-octylglucoside. In intact BBMV the [^{14}C]-PFA binding was measured under completely equilibrated conditions [Na^+_o (or K^+_o),H^+_o = Na_i (or K_i), H^+_i] in order to avoid allostoric cis- and trans- effects, without or with 20 mM phosphate (P_i). [^{14}C]-PFA binding was determined by rapid filtration techniques. In solubilized BBMV extracts [^{14}C]-PFA binding was determined by Sephadex G-50 gel filtration method. Both in intact BBMV and in solubilized BBMV the binding of [^{14}C]-PFA only in the presence of Na^+ was displaced by a molar excess of P_i. [^{14}C]-PFA binding on both preparations was analyzed by Scatchard plot. In intact BBMV the B_{max} = 336 pmoles PFA/mg protein, the K_D = 150 µM; Hill coefficient = 1. For [^3H]-phlorizin binding in the same BBMV B_{max} = 310 ± 37. For [^{14}C]-PFA binding in solubilized BBMV, B_{max} was 168 pmoles/mg protein and K_D = 300 µM. Conclusion: a) Both Na^+-P_i symporters and Na^+-D-glucose symporters are present in comparable numbers (density) in BBM, b) affinity of PFA for Na^+-P_i symporter is similar to affinity of P_i, as approximated from transport measurement, c) the outlined analysis is suited for assessment of number and affinity of Na^+-P_i symporters in renal BBM and its regulatory changes.

69.4

MECHANISM OF Cl SECRETIONS ACROSS THE EQUINE TRACHEA EPITHELIUM. S.M. O'Grady*, G. Tessier and M. Kannan. Dept. of Veterinary Biology, University of Minnesota, St. Paul, MN 55108.

The isolated equine trachea, stripped of serosal muscle, mounted in Ussing chambers and bathed in physiological Ringer's solution generates a serosal positive transepithelial potential (5-20 mV) and short circuit current (Isc) of ~ 50-100 µA/cm^2. Replacement of Cl with gluconate decreases the Isc by 34%. Substitution of HCO_3 with HEPES buffer decreases the Isc by 22%. Addition of serosal amiloride (1mM) also inhibits the Isc to a similar extent as HCO_3 replacement. Measurement of transepithelial NaCl fluxes shows that Na is absorbed (net flux = 1-2 µmol/cm^2 hr) and Cl is secreted (net flux = 2-3 µmol/cm^2 hr). Replacement of HCO_3 causes a 70% decrease in net Cl secretion. Serosal bumetanide (10µM) inhibits about 35% of the net Cl flux. The effects of 8-Br cAMP are inhibited in the presence of 10µM bumetanide. The conclusions based on these results are: i) Approximately 60-70% of the basal Cl secretion is dependent on HCO_3 and inhibited by amiloride suggesting that Na-H/Cl-HCO_3 exchange mediates a large portion of Cl uptake across the basolateral membrane. ii) A qualitative change in the mechanism of Cl uptake occurs under conditions of cAMP stimulation presumably involving the activation of a Na-K-Cl cotransport system in the basolateral membrane.

69.5

NOREPINEPHRINE REGULATION OF EPITHELIAL ION TRANSPORT IN THE PORCINE GALLBLADDER. Michael D. DuVall* and Scott M. O'Grady. University of Minnesota, Department of Veterinary Biology, St. Paul, MN 55108

Porcine gallbladder epithelium, mounted in Ussing chambers and bathed on both sides with physiological saline solution generates has a serosal positive transepithelial potential (0.7-5.3 mV) and a short circuit current (Isc) of 14-79 uA/cm^2. Under basal conditions Na and Cl are absorbed. Secretagogues (vasoactive intestinal peptide, secretin and cyclic-AMP) stimulate Cl secretion and inhibit Na absorption. Norepinephrine (NE), directly blocks these secretagogue effects and inhibits the Isc. Yohimbine (an α_2-adrenergic receptor selective antagonist) inhibits the effect of NE on Isc; whereas prazocin (an α_1-adrenergic receptor selective antagonist) will not. The objective of this research was to elucidate the mechanism of NE action by examining its effects on transepithelial Na and Cl fluxes and Isc. NE causes a significant increase in net Na absorption. Pretreatment with 1mM amiloride (mucosal side) or removal of Cl from the bathing solutions coupled with amiloride pretreatment blocked the effect of NE on Na absorption. Anion replacement experiments suggest that the effect of NE on Isc is Cl dependent. These results suggest that NE, acting via the α_2-adrenergic receptor, stimulates Na absorption. Presumably by increasing the rate of Na-H and Cl-HCO_3 exchange in the apical membrane.

69.6

TRANSEPITHELIAL NA AND CL TRANSPORT IN THE PORCINE DISTAL COLON. Dept. of Vet. Biol., University of Minnesota, St. Paul, MN 55108. T.R. Traynor* and S.M. O'Grady.

Distal colon epithelia, stripped of serosal muscle, was mounted in Ussing chambers and bathed in Ringer's solution, yielding a serosal positive transepithelial potential of 2-4mV and a short circuit current (Isc) of 20-50uA/cm^2. Mucosal amiloride (10uM) decreased basal Isc by abolishing net Na absorption. Serosal addition of vasoactive intestinal peptide (VIP, 20nM) and leukotriene C_4 (LTC_4, 40nM) increased Isc by increasing the serosal-to-mucosal (S-M) Cl flux. Norepinephrine (NE, 0.5uM) increased Isc and the S-M NaCl fluxes. The responses of VIP, NE, LTC_4 and carbachol (CCH) were inhibited when Cl was replaced with gluconate. Pretreatment with tetrodotoxin (TTX) completely inhibited the LTC_4 response. The NE response was dose dependent and prazosin (0.5uM) caused a ten-fold shift in the NE dose-response curve. The replacement of HCO_3 with 20mM HEPES in the presence of acetazolamide (100uM) decreased S-M Na flux, M-S Cl flux and the net Cl flux. From this data the following conclusions can be drawn: (i) Na absorption occurs through an amiloride sensitive Na channel in the apical membrane, (ii) responses due to VIP, LTC_4, NE and CCH are the result of stimulated Cl secretion, (iii) LTC_4 effects on secretum are mediated by enteric nerves, (iv) NE effects are mediated directly through alpha 1 receptors, (v) Cl absorption across the tissue is HCO_3 dependent, (vi) Na secretion is HCO_3 dependent and stimulated by NE.

69.7

NEUROKININS (NKs) STIMULATE SHORT-CIRCUIT CURRENT (Isc) IN RABBIT ILEAL MUCOSA BY INTERACTION WITH A NEURONAL NK-1 RECEPTOR. Kenneth G. Mandel. The Procter & Gamble Co., Miami Valley Laboratories, Cincinnati, OH 45239-8707.

Substance P (SP) stimulates intestinal water secretion in vivo and transiently increases Isc across isolated intestinal epithelia in Ussing chambers. In this study we compared the effect of SP, NKA, NKB, eledoisin (ELE) and SP-methylester (SPMe), on Isc, to determine the subtype and localization of NK receptors. Distal ileum was isolated from male rabbits, stripped of circular and longitudinal muscle, and mounted in Ussing chambers. Ion transport was measured as change in Isc under voltage-clamp conditions. Serosal, but not mucosal addition of NKs, transiently and dose-dependently increased Isc. The observed rank order of agonist potency, SP=NKA>ELE >>NKB, was consistent with interaction at NK-1 receptors. In addition SPMe, a NK-1 selective agonist, elevated Isc, and tissues desensitized to ELE were coordinately desensitized to SPMe. Tetrodotoxin reduced NK-stimulated Isc; however, atropine & hexamethonium had no significant effects, suggesting a noncholinergic neuronal pathway. Bumetanide and $BaCl_2$, but not amiloride, also attenuated SP-stimulated Isc. The results suggest NK-stimulated Isc is mediated via a submucosal neuronal NK-1 receptor, and that this Isc response may represent transient stimulation of net Cl secretion.

69.8

MECHANISM FOR AIRWAY EPITHELIAL WATER TRANSPORT. Irving F. Miller. University of Illinois at Chicago, Chicago, IL 60680

Water transport across the airway epithelium is primarily paracellular, via electroosmosis and osmosis. In the resting state, the cells forming the pore boundaries are swollen, and the junctions between cells are closed. Active basolateral Na^+-K^+ exchange accompanied by passive basolateral NaCl entry results in accumulation of Cl^- within the cells. Leakage of Cl^- into the lumen and absorption of Na^+ from the lumen results in a potential gradient, lumen negative, across the tissue. Upon stimulation, apical membrane permeability increases, resulting in transport of ions and water into the lumen. The cells shrink, opening small cation-selective intercellular spaces. Na^+-coupled hyperosmotic electroosmotic flow through these spaces creates an osmotic gradient that transports water, primarily through relatively non-selective large pores. Thus, water transport is directly coupled to Cl^- transport, and impaired Cl^- transport, as occurs in cystic fibrosis, directly results in impaired water transport.

SHOCK

70.1

CALCIUM FLUX IN SKELETAL MUSCLE DURING SEPSIS. J. Bhattacharyya*, B. Ugarte*, and M.M. Sayeed. Loyola Univ. Med. Ctr., Maywood, IL 60153

This study investigated skeletal muscle intracell Ca^{2+} regulation during sepsis resulting from an intraabdominal abscess. To produce abscess, we prepared fecal pellets inoculated with E. coli(10^2CFU) and B. fragilis(10^6CFU) and implanted them into abdomens of fasted male Sprague-Dawley rats (≈110g). Sham rats were implanted with sterile fecal pellets. Rectal temp., body wt., food consumption and mortality were monitored in rats daily for 5 days after implantations. To measure Ca^{2+} flux, isolated rat soleus muscles at resting tension were incubated in Kreb's medium with ^{45}Ca. Ca^{2+} flux into intracell compartment [nmol/(hrxg)] was determined after washing off muscle's extracell ^{45}Ca using La^{3+}. 40% of septic rats but no sham rats died by day-2 post-implantation; no deaths occurred in the sham or the septic group from day-3 to day-5. Rectal temp. increased and body wt. and food consumption decreased on day-1 but they returned toward control levels between day-2 and day-5 in both sham and surviving septic rats. The return to control was much slower in the septic group. Ca^{2+} flux in septic muscles [405±36(n-11) on day-2, 405±57(n-7) on day-3] appeared elevated compared to sham [275±25(n-8) on day-2, 314±43 on day-3]. The sepsis-related increase in skeletal muscle Ca^{2+} flux may be associated with altered intracell Ca^{2+} level and is similar to that reported previously in the skeletal muscle of bacteremic rats. (Support:NIH Grants GM32288, HL31163)

70.2

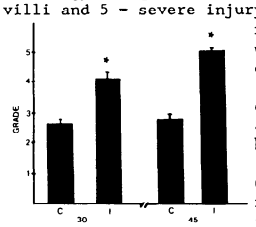
LEUKOTRIENE B_4 AND LYSOSOMAL ENZYMES AFTER REVERSIBLE GLOBAL HEPATIC ANOXIA. P.A. Schaefer*, M. Rosalis*, F.B. Cerra*, F.N. Konstantinides*, and A. DiBenedetto* (SPON: A.M. Spanier) Depts. of Surgery, Nassau County Medical Center, East Meadow NY 11554, and University of Minnesota, Minneapolis MN 55455.

Leukotriene B_4 (LTB) is an important mediator in pathophysiological processes, inducing in vitro lysosomal enzyme release. Our previous work showed increased liver LTB levels after 90 min reversible global hepatic anoxia in a canine model. The present study proposed to determine the pattern of LTB levels and liver lysosomal enzyme release in vivo. Just after reperfusion, the hepatic vein plasma levels of N-acetyl-beta-glucosaminidase, beta-glucuronidase, and cathepsin B rose to 10-20x baseline (140, 1150, 35 nmoles $ml^{-1}hr^{-1}$, respectively). These levels then dropped at 15 min and returned to even higher levels by 60 min. Over the same time interval, liver LTB levels rose to a maximum (2½x) after reperfusion, then fell to baseline by 60 min. Concurrently, aspartate aminotransferase levels rose 20x by 20 min, followed by ornithine carbamoyl transferase (5x at 60 min), indicating hepatocellular damage. These data suggest that hepatic anoxia provokes both LTB generation and lysosomal enzyme release in the liver, preceding indications of liver cell injury. Because the liver is also known to clear leukotrienes and lysosomal enzymes from plasma, these findings further suggest impairment of clearance mechanism(s) in response to anoxia, thus possibly exacerbating tissue injury.

70.3

INTERMITTENT ISCHEMIA POTENTIATES INTESTINAL REPERFUSION INJURY. E.T. Clark* and B.L. Gewertz. University of Chicago, Chicago, IL 60637

We tested the hypothesis that intestinal reperfusion injury is exacerbated by multiple episodes of ischemia. Denervated isoperfused rat small intestines (n=16) were subjected to either 30 or 45 min of flow interruption. Ischemia was continuous (C, single episode) or intermittent (I, multiple 15 min episodes separated by 5 min reperfusion). Histologic sections were obtained after each ischemic insult and following one hr of reperfusion. Histology was graded in a blinded fashion with 1 = normal villi and 5 = severe injury. Intermittent episodes of ischemia resulted in significantly worse histologic injury than comparable continuous ischemic intervals. This damage occurred during the 1 hr reperfusion period as immediate post-ischemic histologies were not different (30 min: C,2.1 ± 0.2 vs I, 2.3 ± 0.4; 45 min: C,2.8 ± 0.3 vs I, 3.2 ± 0.4). Even short periods of reperfusion during an ischemic insult greatly increased mucosal injury. These observations may explain the poor outcomes in patients with mesenteric ischemia who suffer multiple ischemic episodes.



70.4

LETHAL EFFECTS OF BETA BLOCKERS AND CALCIUM ANTAGONISTS. J. Vick (SPON: E. Triantaphyllopoules). FDA, Washington, DC 20204

A series of minipigs and Beagle dogs were used to study the pharmacological effects of selected calcium antagonists alone and in combination with propranolol. Animals were anesthetized and instrumented to record vital physiological functions. Verapamil was administered I.V. (0.5 mg/kg) with and without (0.5 mg/kg) of propranolol. Verapamil alone produced bradycardia, hypernea, and a modest decrease in blood pressure. In contrast verapamil after propranolol produced marked hypotension, severe bradycardia, A-V blockade and death in 8 of 8 animals. Nifedipine produced effects similar to verapamil except that the dose required to produce a lethal interaction with propranolol was less (0.05 mg/kg). Also, no A-V blockage was observed with nifedipine. Diltiazem alone or in conjunction with propranolol also produced effects similar to verapamil except that, like nifedipine, A-V blockage was not observed. Nisoldipine and nimodipine alone in doses of from 0.5 to 0.1 mg/kg produce immediate cardiovascular failure characterized by a precipituous fall in arterial blood pressure, profound bradycardia, respiratory depression, A-V blockade, and death. Non lethal doses (0.05 mg/kg) of either drug in combination with propranolol (0.5 mg/kg) produces death in both minipigs and dogs similar to that observed with the other blocking drugs. The observed lethal effects of a combination of propranolol and a calcium channel blocker could be reversed by calcium chloride.

70.5

SURGICAL PROPHYLAXIS FOR PULMONARY EMBOLISM. Kenneth G. Swan. UMDNJ-New Jersey Medical School, Newark, N.J. 07103-2757.

Over a 12 month period (July 1985-July 1986) 12 patients on the Trauma Service at our institution suffered fatal pulmonary emboli. The nature and severity of their injuries precluded the use of calf compression boots, mini-dose heparin or full anticoagulation in many instances. In response to this alarming incidence of fatal pulmonary embolism we employed Greenfield filters prophylactically in those patients considered to be at high risk for development of deep venous thrombosis and pulmonary embolism. High risk categories included patients with pelvic fractures, head injuries, multiple lower extremity fractures (preventing evaluation of venous thrombosis), age greater than 40 years, past history of deep venous thrombosis and presence of spinal cord injuries. We inserted 65 inferior vena caval filters; 60 were via an internal jugular venous route and five via a femoral venous route. There was no mortality. Morbidity was seen in one patient who developed ipsilateral deep venous thrombosis after a femoral venous insertion. One filter migrated to the left inferior pulmonary artery, uneventfully. Follow-up demonstrated a zero pulmonary embolism rate. We believe those trauma patients who cannot undergo adequate evaluation of deep venous thrombosis or cannot tolerate potential complications of anticoagulation, should be offered Greenfield filter placement with assurance that morbidity and mortality will be extremely low and that threat of death from pulmonary embolism will be eliminated.

70.6

CONTINUOUS ARTERIOVENOUS HEMOFILTRATION (CAVH) AS THERAPY FOR SEPSIS-INDUCED ACUTE LUNG INJURY IN IMMATURE SWINE. P.A. Lee and J.R. Matson*, Oklahoma Medical Research Foundation, Oklahoma City, OK 73104 and Humana Hospital-Medical City, Dallas, TX 75230

The purpose of this study was to evaluate the effect of CAVH therapy on morbidity and mortality associated with sepsis induced lung injury. This technique selectively filters plasma components up to 20kD MW out of the blood. Included in this Molecular weight range are IL-1, TNF monomer and toxic shock toxins. Studies were performed on 16 (9 treated, 7 control) anesthetized swine receiving and LD_{100} IV infusion of live Staphylococcus aureus (S.aureus; 7 x 10^9 organisms/kg) over 1 hour. Animals were monitored for 36 hours. In the treated group, CAVH was initiated immediately after the bacterial infusion and continued for six hours at an ultrafiltration rate of 500ml/hr. Control animals developed early physiologic changes associated with S. aureus sepsis including marked hyperventilation, hypoxemia and reduced cardiac output. Mean survival time in this group was 30 hours. Survival time in CAVH-treated animals was significantly greater (200%); animals exhibited only mild hyperventilation and slightly decreased cardiac outputs. PaO_2 was significantly than pre-treatment values during CAVH therapy and returned to baseline by the tenth hour. We conclude that CAVH therapy transiently improves pulmonary function and prolongs survival in this sepsis model.

Supported by Humana Advanced Surgical Institutes, Dallas, TX

SKELETAL MUSCLE PHYSIOLOGY

71.1

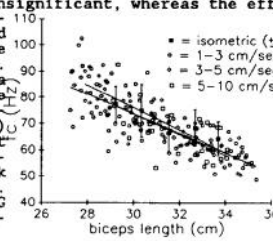
BW A1433, AN ADENOSINE RECEPTOR ANTAGONIST, REVERSES THE DEPOLARIZATION INDUCED BY HYPOXIA IN IN VITRO HAMSTER DIAPHRAGM MUSCLE. Sharon A. Esau. University of Virgina, Charlottesville, VA 22908

Hypoxia depolarizes the diaphragm membrane in vitro. Theophylline reverses the depolarization. We hypothesized that theophylline was acting as an adenosine blocker, rather than by phosphodiesterase inhibition. To test this hypothesis we studied the effect of BW A1433 (Burroughs-Wellcome), an adenosine antagonist with no phosphodiesterase inhibiting activity, on membrane potential (E_m) in nonhypoxic and hypoxic muscle from normal and chronically hypoxic animals. Muscle strips were studied in Krebs solution at 37°C. For nonhypoxic studies the bath was aerated with 95% O_2, 5% CO_2, for hypoxia studies 21% O_2, 5% CO_2 was used. E_m was measured using 3M KCl filled glass microelectrodes. In nonhypoxic muscle from normal animals BW A1433 (100 mcg/l) produced a slight hyperpolarization of -4 ± 1mV. With acute hypoxia E_m decreased from -77 ± 2 mV in control conditions, to -72 ± 2 mV ($p<.001$). The addition of BW A1433 returned the membrane to a resting potential of -79 ± 3 mV($p<.001$). Muscles from chronically hypoxic animals had an E_m of -76 ± 1 mV in nonhypoxic conditions and did not change with acute hypoxia or BW A1433. Thus, the decrease in E_m induced by acute hypoxia is mediated by adenosine and can be reversed by adenosine blockers with no phosphodiesterase inhibiting activity.

71.2

EFFECT OF FORCE (F), LENGTH (L) AND VELOCITY (V) ON THE CENTER FREQUENCY (fc) OF THE EMG POWER SPECTRUM. S. Romano* J. Walsh and A. Grassino. Ist. Fisiopatologia Respiratiria CNR, Palermo, Italy, Meakins-Christie Labs, McGill University and Notre Dame Hosp. Montreal, Canada.

We examined the EMG of the biceps brachii in 6 subjects with surface electrodes. Subjects performed 3 maximum voluntary isometric contractions (MVC) followed by a series of contractions at 10 to 50 %MVC. Each series was performed 3 times at 60 (short muscle), 75, 90, 105 and 120 deg. (long muscle) of elbow flexion. Isometric contractions of 5 seconds were used to evaluate the role of F and L. In non-isometric contractions the subjects lifted a weight at various velocities, over an angle range of 170 deg to 10 deg to evaluate the effect of V and L. For each 256 ms of EMG signal the fc was determined. Multiple linear regression was performed on isometric and non-isometric contractions. In all subjects the effect of F and V on fc was small or insignificant, whereas the effect of L was large and significant. The fc decreased with increasing muscle length as seen in the fig. for one subject. With a 20% shortening in muscle length (similar to the diaphragm tidal shortening) the fc increases by about 31%. Therefore, intrabreath shortening may mask intrabreath decay in fc. We propose intrabreath EMG analysis should be performed at iso-length.



71.3

WITHDRAWN

71.4

Type of contraction affects maximal blood flow and $\dot{V}O_2$ in isolated, contracting muscle. S.Dodd, E.Brooks*, D.Hestens*, P.Crawford, & S.Powers. Louisiana State University, Dept. of Kinesiology & School of Vet. Med. Baton Rouge, LA 70803.

We used the isolated gastrocnemius-planteris preperation in 6 dogs to determine the effects of isometric twitch and tetanic contractions on maximal $\dot{V}O_2$ and blood flow($\dot{Q}$). The muscle was stimulated at 5-6 Twitches/sec (under normoxia and hypoxia), 1 Train/sec (200ms-50Hz), 1 Train/sec (300ms-70Hz) & 2 Trains/sec (100ms-50Hz) for 5 min. Twenty min. was given between treatments and their order was counterbalanced. Arterial and venous blood were sampled and $\dot{Q}$ taken during the last min. of contractions for determination of $\dot{V}O_2$. The $\dot{V}O_{2max}$, $\dot{Q}_{max}$, and the extraction ratio for oxygen (ER) were as follows:

	$\dot{V}O_{2max}$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)	$\dot{Q}_{max}$	ER (Ca02-Cv02/Ca02)
5-6 Tw-Normoxia	10.7±1.3	92.4±10.4	.69±.03
5-6 Tw-Hypoxia	7.4±1.6*	112.8±12.4*	.90±.04*
1Tr-200ms-70Hz	14.7±2.3*	111.5±21.2*	.76±.05
1Tr-300ms-50Hz	12.3±2.3*	107.1±18.7*	.74±.06
2Tr-100ms-70Hz	13.7±1.9*	118.9±15.3*	.72±.04

Values are ±SEM *-Sig. diff. from 5-6 Tw normoxia ($p<0.05$)

These data suggest that in isolated, contracting muscle 1) a vasodilatory reserve exists during maximal twitch contractions as shown by the imposition of hypoxia, & 2) 1-2 Trains/sec elicit a greater $\dot{Q}$ & $\dot{V}O_2$ than twitch contractions.

This study supported by The Am. Heart Assoc.-LA Affiliate

71.5

PORCINE MALIGNANT HYPERTHERMIA (MH): REACTION OF PIGLETS TO HALOTHANE. Randi B. Fay*, and Esther M. Gallant. Department of Veterinary Biology, University of Minnesota, St. Paul, MN 55108.

MH susceptible (MHS) piglets of less than 8 weeks of age do not usually develop limb muscle rigidity in response to a brief halothane exposure (5 min, 3%). Genetically MHS and normal 4-5 week old piglets were exposed to a brief halothane challenge and to 30 min of halothane combined with succinylcholine (H+SCh). Only two of eight MHS piglets developed limb rigidity in response to halothane alone or on subsequent exposure to H+SCh after thiamylal induction. However, all MHS piglets (and no normal piglets) developed clinical signs of MH initiation during 30 min of H+SCh. Temperature of MHS piglets rose from 99.4±0.5 to 101.4±1.0°C while it fell slightly in normal pigs. Venous pH fell from 7.46±0.02 to 6.88±0.07 while pCO_2 rose from 36±2 to 126±17 torr in MHS pigs, and plasma $[K^+]$ rose from 4.0±0.1 to 7.1±0.6 meq. Muscles removed from these piglets prior to H+SCh were exposed to halothane in vitro. MHS muscles responded with characteristic depression of tetanus and prolonged relaxation time but did not develop contractures. We conclude that in the absence of either halothane-induced limb rigidity or in vitro contractures these young animals were still susceptible to fatal MH episodes on exposure to appropriate triggering agents. (Supported by the Minnesota Agricultural Experiment Station and the Minnesota Veterinary Medical Council.)

71.6

EFFECTS OF PERCHLORATE ON MAMMALIAN SKELETAL MUSCLE CONTRACTILE RESPONSES. Naomi S. Taus*, Virginia M. Goettl*, Linnea Lentz* and Esther M. Gallant. Department of Veterinary Biology, University of Minnesota, St. Paul, MN 55108.

Perchlorate (ClO_4^-) appears to act in amphibian skeletal muscle as a facilitator of EC coupling causing a lowering of the activation threshold which is suggested to be due to a shift in the threshold for charge movement (Luttgau et al, 1983). We have investigated whether ClO_4^- action in mammalian skeletal muscles is consistent with the same mechanism. Both twitch and potassium contracture magnitudes were increased in mouse edl muscles treated with 5 mM ClO_4^-. However, the activation threshold for K-contractures with and without ClO_4^- was not different. Tetanus force was not altered in either edl or soleus muscles; however, the relaxation phase was prolonged by ClO_4^-. In porcine skeletal muscles, similar effects were seen on twitch and tetanus, and the tetanus rise time was significantly shorter in the presence of ClO_4^-. Caffeine also lowers the activation threshold and potentiates K-contractures of amphibian muscles. However, in mouse edl muscles caffeine potentiated K-contracture magnitude without altering the activation threshold. Thus, it appears that neither agent has identical effects in amphibian and mammalian skeletal muscles, and that the action of ClO_4^- might involve a mechanism other than a shift in the charge movement threshold. (Supported by MDA and the U of M UROP program.)

71.7

AEQUORIN-INJECTED SINGLE SKELETAL MUSCLE FIBERS PROVIDE A QUANTITATIVE METHOD FOR THE STUDY OF MYOFIBRILLAR RESPONSIVENESS TO Ca^{++} IN INTACT CELLS. J.D. Hannon* (SPON: J.R. Blinks). Dept. of Pharmacology, Mayo Foundation, Rochester MN 55905.

Skinned muscle fibers have been widely used to study directly the relation between $[Ca^{++}]$ and tension under various circumstances. However, one would not expect the effects of membrane-derived second messengers or of other soluble cytoplasmic constituents to persist in skinned fibers, and the question has been raised as to whether myofibrillar responsiveness to Ca^{++} is ever normal in such preparations. The relation between intracellular $[Ca^{++}]$ and tension has been studied in ordinary twitch contractions of aequorin-injected heart muscle, but this approach has the disadvantages that there are unknown kinetic lags in both the $[Ca^{++}]$ and tension signals, and $[Ca^{++}]$ gradients are probably set up within the cell when $[Ca^{++}]_i$ changes rapidly. Low-sodium contractures of aequorin-injected heart muscle have been used to avoid some of these problems, but oscillations of $[Ca^{++}]_i$ can be troublesome, and the calibration of aequorin signals in multicellular preparations of cardiac muscle is much less reliable than in intact single frog skeletal muscle fibers (ISFSMF). Since the K^+ contractures of ISFSMF are long-lasting and reproducible, and their strength can be graded at will, we attempted to use them for the quantitative study of myofibrillar responsiveness to Ca^{++}. ISFSMF from t. anterior of R. temporaria were microinjected with aequorin. Isometric tension and aequorin signals were monitored as the $[K^+]_o$ of the physiological saline solution was increased to levels between 17.5 and 35 mM (K·Cl product constant). At the end of the experiment the fiber was lysed with Triton X-100 for calibration, and estimates of $[Ca^{++}]_i$ were back-corrected for aequorin consumption. A consistent relation between tension and $[Ca^{++}]_i$ was obtained in repeated contractures, and Fourier analysis showed no high-frequency peaks in either signal. This relation was altered reversibly in the direction of increased myofibrillar responsiveness to Ca^{++} by sulmazole and (-)-pimobendan. Support: USPHS Grant HL12186.

CARDIAC MUSCLE PHYSIOLOGY

72.1

TEMPERATURE DEPENDENCE OF EXCITATION-CONTRACTION COUPLING IN ISOLATED RAT MYOCYTES. David L. Groden*, Zhen Guan*, Bruce A. Biagi, Ruth A. Altschuld*, and Bradford T. Stokes. Ohio State University, Columbus, OH 43210.

To examine the effect of temperature on excitation-contraction coupling, single cardiac myocytes were isolated from 3-month-old normal rats. When myocytes were impaled with standard microelectrodes and perfused with 1 mM Ca^{++}, Krebs-Henseleit buffer at $[K^+]_o$ of 6.0 mM, resting membrane potential was -62±2 mV (mean±SEM) at 21°C as compared to -71±2 mV at 37°C ($p<0.05$). In addition, APD_{50} was significantly prolonged ($p<0.0005$) at 21°C (52.0±4.4 msec) when compared to 37°C (22.2±4.5 msec). Cytoplasmic free Ca^{++} transients measured by fura-2 fluorescence microscopy demonstrated a half-relaxation time of 171±13 msec at 30°C, as opposed to 133±11 msec at 37°C for beat #1 and 222±15 msec vs. 129±18 msec for beat #5 ($p<0.05$). Similarly, for beats 1, 5 and 10 of a stimulation train, photodiode edge detection revealed significant prolongation of the time to peak shortening, time to 50% relaxation, and time to 80% relaxation at room temperature ($p<0.0001$). These data point to temperature-dependent effects on sarcolemmal currents and intracellular Ca^{++} handling which modulate contractile dynamics in isolated myocytes. (Supported by Central Ohio Heart Chapter, Inc.)

72.2

STARLING'S LAW OF THE HEART: THE STRETCH-INDUCED INCREASE IN THE Ca^{++}-AFFINITY OF TROPONIN C IS THE RESULT, NOT THE CAUSE OF INCREASED CROSS-BRIDGE ATTACHMENT. Jianxun Wang*, Norman K. Lee*, and John R. Blinks. Department of Pharmacology, Mayo Foundation, Rochester MN 55905.

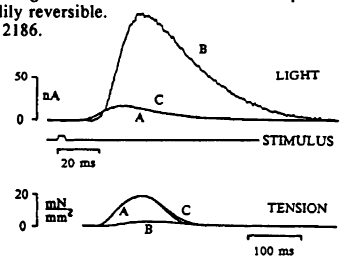
Stretch increases the degree of activation of cardiac muscle without increasing the amplitude of the intracellular Ca^{++} transient. In skinned muscle fibers stretch shifts the steady-state pCa-tension curve to lower $[Ca^{++}]$, and it has been suggested that this may explain increased tension development in twitches. However, there is also evidence that the Ca^{++}-affinity of troponin C (TnC) is increased by cross-bridge attachment; the stretch-induced increase in affinity might be secondary to that. Because the timing of changes in the Ca^{++} transient should distinguish between these possibilities, we studied the influence of changes in fiber length on the time course of the Ca^{++}-transients associated with isometric contractions of aequorin-injected cat and ferret papillary muscles. The aequorin signal of the first contraction after a sudden diastolic change in muscle length does not differ from the previous signals until shortly before its peak (5-10 ms after the onset of tension development); after that the change has the characteristics that one would expect if increased cross-bridge attachment caused TnC to be a more effective Ca^{++} sink (a slight decrease in peak light and an earlier decay of the aequorin signal). Force development can be abolished in the continued presence of the Ca^{++} transient by application of hypertonic solutions, by substitution of D_2O for H_2O, or by 2,3-butanedione monoxime, all of which are thought to interfere with cross-bridge attachment. With all of these interventions, the influence of fiber length on the aequorin signal decreased progressively with decreasing tension development, and disappeared when tension development was abolished. These findings suggest that fiber length has no influence on the Ca^{++}-affinity of TnC in the resting muscle, and that the changes observed in skinned muscle fibers are secondary to increased cross-bridge attachment. Support: HL12186.

72.3

DEUTERIUM OXIDE SLOWS THE Ca^{++}-TRANSIENT AND GREATLY INCREASES ITS AMPLITUDE WHILE DEPRESSING TENSION DEVELOPMENT IN THE FERRET PAPILLARY MUSCLE. John R. Blinks and Jianxun Wang*. Pharmacology Dept., Mayo Fdn., Rochester MN 55905.

In intact frog skeletal muscle fibers the substitution of D_2O for H_2O in the bathing medium abolishes tension development in twitches and tetani, and greatly reduces the amplitude of the intracellular Ca^{++} transient; in skinned fibers myofibrillar Ca^{++}-sensitivity is decreased, though maximum tension development is increased (Allen, Blinks, & Godt, J. Physiol. 354, 225, 1984). In contrast, we find that in aequorin-injected ferret papillary muscles D_2O substitution greatly increases the amplitude of the aequorin signal, while nearly abolishing tension development. D_2O substitution does influence the aequorin reaction, but in ways that would be expected to decrease the amplitude of the aequorin signal somewhat. Thus the amplitude of the Ca^{++} transient is clearly increased. The onset of the aequorin signal is also delayed, and the Ca^{++} transient is prolonged, suggesting a reduction in the rate of Ca^{++} sequestration. All of these effects are readily reversible.

Support: USPHS Grant HL12186.



Records from an aequorin-injected ferret papillary muscle (L_{max}, 31° C, 15/min, 40 signals averaged)

A: control, in H_2O

B: in D_2O (99.8%)

C: after return to H_2O

72.4

$[Ca^{2+}]$ ENHANCES RYANODINE DEPRESSION OF TENSION TRANSIENTS IN SKINNED MYOCARDIAL FIBERS OF THE RABBIT. Judy Y. Su* (SPON: A.M. Gordon). Univ. of Washington, Seattle, WA 98195

Ryanodine binds to a high affinity site of isolated SR. It depresses the caffeine-induced tension transient of the subsequent Ca loading-release cycle of skinned muscle fibers if present when the SR Ca channel is open. This study tests whether this ryanodine effect is sensitive to $[Ca^{2+}]$ as is ryanodine binding. Fiber bundles from homogenized, skinned papillary muscle were dissected and mounted for force measurement. A Ca loading-release cycle of the SR was performed using a Ca loading solution, and then a releasing solution containing 25 mM caffeine and the area of the resulting tension transient (TT) measured. Each experiment consisted of three cycles: a control (C_1, no ryanodine), followed by a test (± 1 μM ryanodine ± caffeine in the releasing solution with pCa > 8, 7.5 - 5.0), and finally a second control (C_2, no ryanodine). The TT/C_2 area was expressed as a percent of TT/C_1. Without caffeine, ryanodine depressed TT/C_2 only at pCa < 5.5. With caffeine to activate the Ca channel, the ryanodine depression of TT/C_2 was enhanced by $[Ca^{2+}]$ with the ED_{50} of pCa 7.0. These results agree with that of ryanodine-receptor binding in isolated SR and suggest that the depression is enhanced by ryanodine binding especially when the Ca channel has been opened by caffeine. (Supported by NIH HL20754).

72.5

BETA RECEPTOR DERANGEMENT IN VENTRICULAR ANEURYSM. LB McGrath*, JM Levett*, J Bianchi. Deborah Research Institute, Browns Mills, NJ 08015-1799

The study was designed to determine if any alteration in receptor density was associated with ventricular aneurysms. Human myocardium removed in the surgical treatment of ventricular aneurysm was divided into three samples: (control), subendocardial perianeurysm (PERI), and infarcted aneurysmatic tissue (INF). Tissue was homogenized in Tris maleate buffer (80 mM, pH 7.2) and differential centrifugation produced a fraction enriched in sarcolemmal membrane. Membranes were incubated for 15 min with radio-labeled dihydroalprenolol, clonidine, and N-methyl -quinuclidinylbenzilate. Binding was stopped by addition of ice-cold buffer followed by rapid filtration. The results represent specific binding in fmol/mg membrane protein.

	n	Beta	Alpha	Muscarinic
Control	8	45.2±1.5	19.6±1.4	8.0±0.8
PERI	8	67.5±1.3	10.5±1.6	4.0±0.4
INF	8	28.1±1.4	8.1±0.8	2.5±0.5
p*		0.0003	0.0015	0.0027

values are Mean + SEM; data analyzed by two way ANOVA

Only the beta analog demonstrated enhanced binding around the aneurysm indicating that the events of infarction and aneurysm formation can alter receptor density which may affect cellular response, contributing to arrhythmogenesis.

72.6

ANGIOTENSINOGEN CONVERTING ENZYME (ACE) INHIBITORS IMPROVE FUNCTION OF DOG HEART DURING AND AFTER A SHORT PERIOD OF REGIONAL ISCHEMIA. H. Zheng, N. Bittar, *L. Chudej, and *J. Koke. Dept. Med., U. Wisconsin, Madison, Wisconsin, 53792; and *Dept. Biol., S. W. Texas State U., San Marcos, Tx., 78666.

The ACE inhibitors captopril (CAP 0.5 mg/kg), enalapril (ENA, 1.0 mg/kg), enalprilat (ENP, 1.0 mg/kg), and lisinopril (LIS, 1.0 mg/kg) were infused into the left anterior descending coronary artery (LAD) of dogs 5 minutes prior to and during a 15 minute occlusion of the LAD proximal to the infusion site. The ischemic period was followed by a 30 minute period of reperfusion (RP). The effects were compared to those resulting from infusion of superoxide dismutase (S) and catalase (C), and to infusion of saline (SHM). The following results were obtained for segment shortening in the region made ischemic (diastolic length - systolic length / diastolic length x 100).

Exp.	ISCHEMIA	0-10 RP	15-30 RP
SHM	-6.8 +/- 1.4	6.8 +/- 3.2	2.1 +/- 2.2
S+C	-6.1 +/- 1.8	19.4 +/- 2.3s	7.0 +/- 2.3s
CAP	0.6 +/- 1.8s	13.9 +/- 2.8s	13.4 +/- 2.9a
ENA	-3.7 +/- 2.3s	8.4 +/- 1.9	9.9 +/- 1.8s
ENP	-0.8 +/- 1.8s	7.8 +/- 2.3	8.5 +/- 2.2s
LIS	-0.8 +/- 1.6s	11.1 +/- 2.1s	8.9 +/- 1.7s

The values are % control +/- SEM; significant differences (P < 0.05) from the sham group are indicated by "s"; from all other groups by "a". These results suggest the ACE inhibitors prevent some of the loss of contractility during ischemia, and also accelerate recovery during reperfusion.

72.7

ANGIOTENSINOGEN CONVERTING ENZYME (ACE) INHIBITORS IMPROVE RECOVERY OF RAT HEART AFTER A SHORT PERIOD OF REGIONAL ISCHEMIA. D. Vaughan, D. Yu, N. Bittar, and *J. Koke. Dept. Med., U. Wisconsin, Madison, Wisconsin, 53792; and *Dept. Biol., S. W. Texas State U., San Marcos, Tx., 78666.

We perfused groups (n=6 each) of isolated, working rat hearts with solutions containing 0.5 mg/l captopril (CAP) and 1.0 mg/l enalaprilat (ENA). These were compared to groups (n=6) of hearts perfused without ACE inhibitors (SHM) and to hearts perfused with solutions containing superoxide dismutase (S) and catalase (C). After isolation, hearts were subjected to 15 minutes of regional ischemia (I) by temporary occlusion of the left coronary artery, followed by 30 minutes of reperfusion (RP). Aortic output (AO), left ventricular pressure (LVP), and dP/dT of LVP were recorded at intervals, as follows:

Exp.	AO	dP/dT	LVP
SHM 15m I	44.9 +/- 7.0	77.3 +/- 1.1	60.5 +/- 2.0
S+C 15m I	44.7 +/- 15.1	77.7 +/- 8.5	82.6 +/- 12.0s
CAP 15m I	39.8 +/- 4.8	83.9 +/- 2.3	91.0 +/- 3.1s
ENA 15m I	66.5 +/- 4.8a	89.5 +/- 3.5	89.5 +/- 3.2s
SHM 30m RP	43.3 +/- 3.0	71.0 +/- 5.3	75.8 +/- 1.4
S+C 30m RP	152. 0 +/-24.8a	101.3 +/- 13.5s	134.7 +/- 10.2a
CAP 30m RP	45.1 +/- 2.9	82.9 +/- 2.1s	91.2 +/- 2.2s
ENA 30m RP	67.7 +/- 4.8s	94.0 +/- 3.5s	90.2 +/- 3.0s

The values are % control +/- SEM; significant differences (P < 0.05) from the sham group are indicated by "s"; from all other groups by "a". These results indicate ACE inhibitors improve cardiac function during ischemia and accelerate recovery during reperfusion.

72.8

Thermodynamic studies on normal (norm.) and thyrotoxic (thytx) cardiac myosin using Kinetic and calorimetric measurements. *G. Kaldor and D. Hoak, VAMC, Allen Park, MI. 48101 and Dept. of Pathology of Wayne State University, Detroit, MI. 48201*

As compared to the norm. cardiac myosin, calorimetric measurements showed, that the interactions of thytx cardiac myosin-ATP involved significantly larger enthalpy, entropy and heat capacity changes. (Norm: H^*=-10.800, S^*=17.5,Cp=240. Thytx: ΔH^*=-16.000, ΔS^*=43,Cp=350). The same pattern emerged with the Kinetic studies. (Norm: $\Delta H^{\ddagger}$=-7000, $\Delta S^{\ddagger}$=3.5 . Thytx: $H^{\ddagger}$=-13.000, $\Delta S^{\ddagger}$=29). The Kinetic studies also revealed that the thytx cardiac myosin had a higher energy of activation A+=-14.000) but a lower negative entropy change ($\Delta S^{\ddagger}$=-21) than the norm. protein ($\Delta A^{\ddagger}$=-10.600, $\Delta S^{\ddagger}$=-37). The magnitude of the observed heat capacity change indicated that the binding of ATP caused a conformational change on the myosin molecule (EFTINK,MR ET AL BIOCHEMISTRY 22, 3884 1983). As compared to the norm. the results of this study suggest a large or different ATP induced conformational change in the thytx molecule. The $\Delta S^{\ddagger}$ decrease following the ATP binding may be the consequence of the constraint put on the rotation of ATP following the binding induced conformational change. Perhaps the ATP induced conformational change on the thytx molecule permitted a faster enzymatic attack on the substrate resulting in higher ATPase activity activity on part of the thytx cardiac myosin.

72.9

SATELLITE CELLS FOR MYOCARDIAL REGENERATION.
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Allegheny-Singer Research Institute, Pittsburgh, PA 15212

Satellite cells are mononucleated myogenic stem cells located under or embedded in the basal lamina of skeletal muscle fibers. The formation of new muscle nuclei and regeneration of injured skeletal muscle from satellite cells have been well documented. Mammalian cardiac myocytes divide and multiply during embryonic and early postnatal life. After this period, growth involves cellular enlargement and proliferation of subcellular organelles. Ventricular muscle cells of adult mammals are terminally differentiated cells which lose their ability to multiply. Injuries to the heart result in scar formation, and the lack of regenerative capacity of cardiac muscle has been attributed to the fact that myocardium does not contain satellite cells. Dogs with humane care and under proper anesthesia were used for satellite cell isolation from tibialis anterior muscle. The heart was subjected to cryoinjury by a cryoprobe maintained at -160°C by internally circulating liquid nitrogen. The isolated satellite cells were cultured and labeled with ^{14}C-thymidine before being implanted back into the injured myocardium of the same dog. After 4 weeks, the injured myocardium had formed a transmural scar with labeled satellite cells surviving between the collagen fibers. After 10 weeks, the implanted satellite cells had proliferated and differentiated into cardiomyocytes. Collagen fibers and satellite cells could still be observed between the newly formed heart muscle cells. This may provide a long-lasting and inexpensive treatment for patients with infarcted myocardium, cardiomyopathy, or ventricular failure.

SMOOTH MUSCLE PHYSIOLOGY AND CELL MOTILITY

73.1

MODIFICATION OF INWARD CA CURRENTS BY CALYCULIN A IN SMOOTH MUSCLE CELLS ISOLATED FROM GUINEA PIG TAENIA COLI.
K. Obara1*, T. Usuki1*, T. Someya1*, H. Yabu1*, H. Ozaki2* and H. Karaki2*(SPON: N. Sperelakis). 1 Sapporo Med. Col., Sapporo 060 and 2Univ. of Tokyo, Tokyo 113, Japan.

Calyculin A (CL-A) is a cytotoxic compound isolated from marine sponges genus Discodermia. CL-A, a potent inhibitor of protein phosphatases, causes contraction and increases cytosolic Ca^{++} concentration ($[Ca^{++}]i$) in rat aorta (Ishihara et al., BBRC and JEPT, 1989). The L-type Ca current is thought to be regulated by the phosphorylation of channel proteins. In the present study, we examined the effects of CL-A on the mechanical responses, $[Ca^{++}]i$ and the voltage-dependent Ca currents in guinea pig taenia coli smooth muscles. $[Ca^{++}]i$ in fura-2-loaded muscles was measured simultaneously with muscle contraction. The voltage-dependent Ca channel currents were recorded by using the patch-clamp technique with the whole-cell configuration. CL-A caused contraction in the absence and presence of external Ca^{++} and increased $[Ca^{++}]i$ in the presence of external Ca^{++}. This increase was inhibited by Ca channel blockers. CL-A increased the voltage-dependent inward currents in a dose dependent manner. Dibutyryl cAMP and isoproterenol did not affect the inward Ca currents. These results suggest that CL-A may facilitate the opening of the voltage dependent Ca channel through the phosphorylation systems other than cAMP-dependent system in guinea pig taenia coli smooth muscles.

73.2

THE AGONIST DEPENDENCE OF THE CA^{2+}-FORCE RELATIONSHIP IN PULMONARY ARTERY SMOOTH MUSCLE.
B.Himpens* and A.P. Somlyo. KUL, 3030 Leuven, Belgium and Univ of Va., Charlottesville, VA 22908.

The relationship between $[Ca^{2+}]_i$, measured with fura-2, and force was investigated in rabbit pulmonary artery during stimulation with high K^+, the α-agonist phenylephrine or the thromboxane mimetic U46619 (9,11-dideoxy -9α,11α -methanoepoxy-PG F_2). During stimulation with high K^+ (1.2 mM Ca^{2+} and 140 mM K^+) $[Ca^{2+}]_i$ reached a maximum of 366 $\pm$ 25 nM, then declined to around 240 nM while force further increased. The EC_{50} of relaxation was 190 nM $[Ca^{2+}]_i$. The Ca^{2+} - force curve followed a three component counter-clock hysteresis loop. 10^{-4} M phenylephrine increased $[Ca^{2+}]_i$ to 246 $\pm$ 16 nM, while the maximum force was similar to that obtained during K^+ depolarisation. The EC_{50} of relaxation was 140 nM. The Ca^{2+} -force relationship described a (two component) counter-clock hysteresis loop with a left shift as compared to the response to 140 mM K . 10^{-7} M U46619 increased $[Ca^{2+}]_i$ transiently to only 170 $\pm$ 16 nM, and force was again comparable to that induced by the t o other stimuli. Its EC_{50} of relaxation was around 120 nM. The U46619/ (two component) counter-clock hysteresis loop showed an even further left shift than phenylephrine. We conclude that both pharmacological agonists used in this study can increase the sensitivity of the regulatory/contractile apparatus to Ca^{2+} Supported by HL15835 to the PMI.

73.3

INTRACELLULAR FREE CALCIUM REGULATION IN SMOOTH MUSCLE CELLS AND CONTRACTILE FUNCTION OF RINGS ISOLATED FROM PIG CORONARY ARTERIES.
C.L. Oltman*, L. Bowman*, M.H. Laughlin and M. Sturek. Dept. of Vet. Biomed. Sci., Dept. of Physiol., and Dalton Res. Ctr., Univ. of Missouri, Columbia, MO 65211.

The purpose of this study was to determine if contractile function and intracellular free Ca^{++} (Ca_i) regulation can be studied in vessel rings and single vascular smooth muscle cells (SMC) isolated from adjacent segments of the same coronary arterial tree. Contractile function was studied in isolated coronary arterial rings (2 mm diameter, 3.5 mm long) mounted on Grass force transducers. The SMCs and coronary arterial rings were isolated from the circumflex coronary arteries of the hearts of 4 Yucatan miniature swine. SMCs were enzymatically dispersed from a segment of the circumflex coronary artery. SMC Ca_i regulation was studied with fura-2 microphotometry within 8 hr of isolation from the artery. The SMC resting Ca_i was 48 $\pm$ 5 nM (n = 43) (X $\pm$ SE). Depolarization with 30 mM KCl caused a predictable 2-fold increase in Ca_i. KCl induced dose related increases in contractile force with an average maximal developed tension 8.5 $\pm$ 0.7 g recorded at doses of 60 - 80 mM KCl. $PGF_2\alpha$ also produced dose related increases in contractile force with maximal force (10.2 $\pm$ 1 g) occurring at a dose of 0.03 mM. Nitroprusside (NTP) produced a dose related relaxation of contractions induced by 30 mM KCl with complete relaxation occurring at a dose of 0.1 mM NTP. NTP (0.001 mM) attenuated the 30 mM KCl induced increase in Ca_i by 25 %. These data indicate that it is feasible to use single SMCs to investigate the cellular mechanisms responsible for the contractile behavior of adjacent segments of coronary artery. Future studies should systematically compare Ca_i in single SMCs and the arterial rings. (Supported by AHA Missouri Affiliate and NIH grant # HL-36531).

73.4

ACTIVE TENSION AND INTRACELLULAR Ca^{2+} IN RESISTANCE ARTERIES OF SPONTANEOUSLY HYPERTENSIVE AND NORMOTENSIVE RATS.
H Xue* and RD Bukoski. Ore Hlth Sci Univ, Portland, OR 97201

Intracellular Ca^{2+} $[Ca^{2+}]$ has been reported as elevated in cultured vascular muscle of the spontaneously hypertensive rat (SHR) compared with the normotensive Wistar Kyoto (WKY). However, phenotypic changes occurring in culture might account for the difference. We have determined $[Ca^{2+}]$ and tension development in mesenteric resistance arteries (MRA) of 7 SHR & 7 WKY, 13 weeks of age (SHR BP=139$\pm$3.5 mmHg; WKY=112$\pm$3, $p<0.001$). MRA were mounted in a wire myograph interfaced with a fluorometer, and equilibrated at 37°C in Hepes-buffered solution (HBS). After wake-up challenges with 100 mM KCl/10 μM norepinephrine (K/NE), basal fluorescence of MRA (ex-340/380 nm; em-510 nm) was determined. MRA were then loaded with 6.6 μM fura-2 AM for 30 min at 37°C. The basal ratio at 340/380 nm was determined, then a challenge with K/NE was given. Calibration constants were determined by addition of 5 mM $CaCl_2$/20 μM ionomycin (R'_{max}) followed by 20 mM Tris-EGTA (R'_{min}) and $[Ca^{2+}]$ was calculated. No inter-strain differences in [fura-2], R'_{max} or R'_{min} were detected. Similarly, no difference in basal $[Ca^{2+}]$ was detected (SHR-58$\pm$12 nM; WKY-50$\pm$11). $[Ca^{2+}]$ during K/NE was greater in SHR than WKY (SHR-151$\pm$19 nM; WKY-87$\pm$21, $p<0.05$) even though active tension development was similar (SHR- 5.8$\pm$0.7 mN/mm; WKY-5.2$\pm$0.7). It is concluded that $[Ca^{2+}]$ may be elevated in SHR MRA during activation, but not the basal state.

73.5

RELEASE OF CALCIUM FROM SARCOPLASMIC RETICULUM IN THYROPATHOLOGIC RAT AORTA. D.B. Stratton and J. Giordano*
Depts. of Physiology and Pharmacology, Drake University, Des Moines, IA 50311

Thyropathology was produced in young male rats by (14) daily i.p. injections of L-thyroxine (200ug) or daily additions of 0.1% propylthiouracil (PTU) to the drinking water. Rings of thoracic aorta were dissected and mounted in tissue baths to record isometric contractions. Contractions were generated in intact rings by addition of 1 uM norepinephrine in calcium-free solution containing 1 uM propranolol. Contractions were induced in saponin-skinned rings by addition of 25 mM caffeine. Thus, contractions in intact rings were solely due to NE-induced receptor-linked calcium release from the sarcoplasmic reticulum (SR); contractions in skinned rings were the result of caffeine-induced calcium release from the SR. Previous studies in this laboratory have shown that response of intracellular contractile substrates to free calcium is unaltered by thyropathology. In both intact and saponin-skinned rings, TRX treatment produced significant decreases in contractile strength as compared to controls; this effect was greater in the intact ring preparation. Contractile responses in rings from PTU-treated rats did not differ from controls. These data suggest the NE-induced decrease in generated tension following TRX treatment is primarily due to a direct effect at the SR, while a lesser component may reflect altered receptor linkage to the SR.

73.6

QUANTITATION OF CALMODULIN AND MYOSIN LIGHT CHAIN KINASE IN SKINNED AND INTACT TRACHEAL SMOOTH MUSCLE. Malu G. Tansey* James T. Stull and Kristine E. Kamm. Dept. Physiology, UT Southwestern Med. Ctr., Dallas, TX 75235

Calmodulin (CaM), myosin light chain kinase (MLCK) and protein contents were quantified in intact and skinned bovine tracheal smooth muscle in order to test the hypothesis that calmodulin (and possibly other regulatory proteins) may be lost during the preparation and the activation of skinned fibers. Muscle fibers were chemically skinned by Triton X-100/freeze glycerination. Homogenates of frozen strips were evaluated for protein content (Bradford) and subjected to SDS-PAGE. The protein content of intact (85 ± 5 μg/mg initial wet wt) and skinned fibers (81 ± 8) was not significantly different. The protein content of skinned and contracted fibers (57 ± 6 μg/mg) was decreased by 30 percent. Myosin, actin, filamin and desmin contents quantified by densitometry of Coomassie-stained gels were the same in intact and skinned fibers. In separate experiments, protein and standards were transferred to nitrocellulose and immunoreacted with antibodies raised against CaM or MLCK. Immunoreactive material was quantified by laser densitometry. Calmodulin content was less in the skinned fibers (276 ± 41 ng/mg) and skinned and contracted fibers (161 ± 26) than in the intact fibers (475 ± 33)($p < 0.05$). However, MLCK values were not different between intact, skinned, and skinned and contracted fibers (362 ± 25, 343 ± 47, 256 ± 33 ng/mg respectively). While calmodulin content was significantly diminished by skinning, tissue concentrations of MLCK and CaM remain three and four orders of magnitude, respectively, above the K_D for CaM activation of MLCK. Therefore, the free calcium concentration is predicted to be the primary regulator for myosin phosphorylation in this model of contractile function. (Supported by NIH HL-32607 and NIH GM07062.)

73.7

INTRINSIC RELAXATION FACTORS AND LENGTH DEPENDENT SENSITIVITY (LDS) IN THE RAT AORTA. J.M. Price, E. Coskinas,* M.D. Sauro,* and D.F. Fitzpatrick.* University of South Florida, Tampa, FL 33612

A possible mechanism for LDS may involve intrinsic relaxation mechanisms in the arterial wall. The objective of this study is to determine the effect of endothelium derived relaxing factor (EDRF) and beta receptor activation on LDS and the length dependence of a naturally occurring relaxing factor, atrial natriuretic factor (ANF). ED50 and ED10 were lower at the length of maximum response (Lmax) than at 80% Lmax with phenylephrine (PHE) and with norepinephrine (NE) before and after endothelium removal. ED10 but not ED50 was lower after endothelium removal at both lengths. The effect of endothelium removal on ED10 was greater at 80% Lmax than at Lmax. ED50, ED10, active stress, and Lmax were lower with NE than with PHE. Relaxation was greater at Lmax than at 80% Lmax with a low dose of ANF but not with a high dose. We conclude that 1. the mechanism for LDS does not involve the endothelium or beta receptors, 2. basal levels of EDRF appear to modulate sensitivity at low levels of activation, (short length or low dose) 3. Lmax depends on the alpha receptor agonist, and 4. the relaxation effect of ANF is length dependent. Supported by NIH grant HL21103 and the American Heart Association, Florida Affiliate.

73.8

TEMPERATURE ALTERS THE EFFECT OF PRELOAD ON THE SENSITIVITY OF VASCULAR SMOOTH MUSCLE (VSM) TO PHENYLEPHRINE. J.T. Herlihy, T.Raabe* and M.J.K. Harper. Univ. of Texas Health Science Center, San Antonio, Texas 78284.

Preload affects the sensitivity (EC_{50}) of VSM to vasoactive agents. The present experiments were performed to determine the temperature dependency of this preload effect. Rat aortic strips were mounted at either high (3.0g) or low (0.75g) preloads in physiologic salt solution maintained at high (37°C) or low (32 or 27°C) temperature. Strips at high preload developed more active force in response to K^+-depolarization and maximum stimulation by phenylephrine than strips at low preloads, presumably because of the length-tension characteristics of the muscle. Temperature had no effect on the K^+ contractures. The maximum responses to phenylephrine also were unaltered at 32°C, but were significantly depressed at 27°C. At 37°C the EC_{50} for phenylephrine was reduced with increasing preload. The preload effect was absent at 32°C and 27°C. These results suggest that the preload-induced change in sensitivity occurs prior to activation of the contractile proteins, perhaps at the level of Ca^{++}mobilization or the agonist/receptor interaction. (Supported by NIH grants HL35391 and HD14048.)

73.9

MYOSIN LIGHT CHAIN (MLC) PHOSPHORYLATION AND MACROPHAGE MOTILITY. Allison K. Wilson and Primal de Lanerolle. Dept. of Physiology & Biophysics, Univ. of IL at Chgo, Chgo, IL 60612.

MLC phosphorylation has been suggested to be part of the mechanism that regulates mammalian nonmuscle cell motility. The level of in vivo MLC phosphorylation is dependent on the balance between the activities of MLC kinase and MLC phosphatases. Previous experiments using the myosin phosphatase inhibitor, okadaic acid, have demonstrated that macrophage motility is highly sensitive to the level of MLC phosphorylation. We have investigated this possibility by determining the effects of proteolytically-digested, constitutively active MLC kinase (MK-I) and of antibodies to MLC kinase on intact macrophages. Electroinjection, the use of voltage discharge to create transient pores in the plasma membrane, was used to incorporate these proteins into macrophages (Fed. Proc. 46:1097, 1987) and the directed chemotaxis assay was used to quantitate motility. The data demonstrate an inverse relationship between an increase in MLC phosphorylation induced by the incorporation of MK-I and cell migration. Triton X-100 extraction assays indicate that a greater proportion of the myosin is associated with the cytoskeleton as MLC phosphorylation increases. Interestingly, inhibition of MLC phosphorylation by the incorporation of antibodies to MLC kinase also decreases the number of cells that migrate. This inhibition of macrophage migration that is observed with both increased and decreased MLC phosphorylation suggests that MLC phosphorylation plays an important role in the regulation of mammalian nonmuscle cell motility.

73.10

EFFECTS OF IONOPHORES ON BIOLOGICAL SYSTEMS. Cindy La Neave*, Keith H. Pannell*, James E. Becvar*, Mahnaz Darvish*, Tim Delmont*, Ralph Kolbeck[1]*, Robert Ginsburg[2]*. (SPON: Dr. Martin Frank) University of Texas at El Paso, El Paso, Texas 79968-0153. [1]Medical College of Georgia, Augusta, Georgia 30912. [2]Stanford Medical School, Stanford, California 94305.

Physiological properties of macrocyclic polyethers (crowns) were investigated in our laboratories using various biological systems to better understand the mechanism with which these compounds interact with membranes. Our interest in these interactions stems from the ability of the macrocycles to encapsulate and transport metal ions. To achieve this we have studied such biological systems as: Luminous Bacteria, Guinea Pig Trachea and Human Coronary Tissue. Our results indicate that these Macrocyclic Polyethers are indeed very powerful manipulators of membrane currents essential for tissue viability. While the larger crowns reversibly inhibit bacterial luminescence, they also possess powerful vasodilation properties on smooth muscle tissue. Preliminary results with the natural ionophores, i.e. Valinomycin, Monensin and X-537A(Lasalocid Acid) indicate that they are active at much lower concentrations. Supported by NIH: Area R15 HL35735, MBRS RR08012, MARC GM 08048.

73.11

MODULATION OF CHOLINERGIC AND ADRENERGIC RESPONSES OF SHEEP ANTRAL SMOOTH MUSCLE BY POTASSIUM CHANNEL BLOCKERS.
Taher Y, El-Sharkawy^ (SPON: J. Welty). Faculty of Medicine, Kuwait University, Kuwait, P.O. Box 24923 Safat, Kuwait 13110.

The effects of blocking potassium channels by cesium and tetraethylammounium (TEA) on the spontaneous contractile activity, and on the responses to muscarinic and beta adrenergic receptor agonists of sheep antral smooth muscle strips were studied. Addition of TEA (5-15mM), 5.9 mM $CsCl_2$, or replacing the K^+ of the Krebs solution by Cs^+ caused a significant increase in the force of the rhythmic spontaneous contractile activity. Carbachol caused a dose - dependent increase in the force of contraction but at high concentrations converted the rhythmic contractile activity to maintained tone. Isopropylnoradrenaline (INA) caused dose - dependent inhibition spontaneous activity. TEA, $CsCl_2$, or Cs^+ substitution for K^+ reversed the excitatory responses to carbachol and attenuated the inhibitory responses to INA. These results suggest that K^+ channels may be involved in the mediation of muscarinic excitation and beta adrenergic inhibition of smooth muscle contractility. This work was supported by grants from Kuwait University and Kuwait Foundation for the Advancement of Science (KFAS).

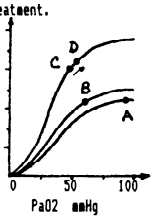
ALTITUDE, HYPERBARIA, CHRONOBIOLOGY

74.1

THE TRIPLE HYPOXIA SYNDROME AND ITS RELATION TO THE OXYGEN CONTENT AT ALTITUDE.
Gustavo R. Zubieta-Calleja, Gustavo Zubieta-Castillo ¶ and Luis A. Zubieta-Calleja ¶.
High Altitude Pathology Clinic (IPPA), La Paz, Bolivia. 2852

The previously described Triple Hypoxia Syndrome (THS) is further analyzed and used to question the validity of the oxygen content formula at high altitude. At sea level the arterial oxygen content, calculated from CaO2 = (Hb) (1.39) (SaO2) + (0.003) (PaO2), for a normal subject, is around 21 Vol%; whereas at 3600 mt in the city of La Paz, a well adapted individual (with physiologic polycythemia) has a CaO2 of around 22 Vol%. Note that an acclimatized person seems to have more oxygen than a sea level individual, a fact previously observed. Patient GAQ, male, 37 years old, 51 Kgs of weight, 157 cm height was diagnosed as suffering from the THS (high altitude hypoxia + increased polycythemia hypoxia + acute inflammatory hypoxia). On consultation he was dyspneic and cyanotic. His hematocrit was 81 % with 9.072.000 red blood cells per cubic mm. and 27 gm% hemoglobin. His blood gases: pH = 7.35, PaCO2 = 32 mmHg and PaO2 = 47 mmHg with a calculated O2 Saturation (SaO2) of 82 %. Following a 24 hr oxygen therapy his pH returned to 7.38 and PaO2 increased to 52 mmHg (SaO2 = 87%). This case permitted the comparison of calculated CaO2 for A) normal subject at sea level, B) high altitude resident and C) increased polycythemic GAQ and D) GAQ after treatment.

	Hb gm%	PIO2 mmHg	PaO2 mmHg	SaO2 %	CaO2 Vol%	Although this patient is suffering from intense hypoxia, the CaO2 is 50 % greater than at sea level. This implies that his oxygen dissociation curve is taller and steeper. It also suggests that the polycythemic at high altitude has plenty of oxygen. Hence, it is the respiratory cascade gradient that counts not the CaO2.
A)	15	150	95	98	21	
B)	17	94	60	91	22	
C)	27	94	47	82	31	
D)	26.6	94	52	87	32	



74.2

MILITARY OPERATIONS AT MODERATE ALTITUDE: EFFECTS ON TOTAL BODY WATER.
D.L. KELLEHER, A.C. HACKNEY*, AND J.A. HODGDON*. Naval Health Research Center, San Diego, CA 92138 and Exercise Physiology Laboratory, UNC, Chapel Hill, NC 27599.

Dehydration degrades work capacity and combat effectiveness. This study evaluated the effect of sustained military operations (SMO) at altitude (2100 to 2900m) on several hydration indices. Subjects were volunteer US Marines conducting training, which included rock climbing, foot marches (4.2 km/day, ~25kg pack load) and infantry maneuvers. Measurements were made at sea level (SL) prior to departing, 12 hrs prior to commencing a 5 day SMO at altitude (AL1), and immediately after the SMO (AL2). Subjects trained at altitude for 11 days prior to AL1 and followed Marine Corps hydration guidelines. Hydration indices included: total body water (TBW) by bioelectric impedance analysis; serum electrolytes; serum and urinary osmolalities (SO, UO); hematocrit (HCT); serum proteins (SP); urine specific gravity (USG); and body weight (BW). Altitude did not affect BW, however, it was significantly reduced by SMO (74.8±2.0 vs 76.0±2.0 kg). Altitude did reduce TBW 8% ($p<.05$); whereas, SMO had no affect. Serum CL^-, K^+, and SP were elevated at altitude (1-6%, $p<.05$). SMO elevated ($p<.01$) HCT (46.2±0.5 vs 45.2±0.6), UO (898±17 vs 557±60 mOsm/kg), and USG (1.024±.001 vs 1.017±.002); Altitude or SMO did not alter SO. The data indicate total body dehydration due to altitude which is not exacerbated by rigorous training. The data also indicate that transient changes in circulating volume can occur during SMO. Supported by Naval Medical Research and Development Command Work Unit M0096.002.

74.3

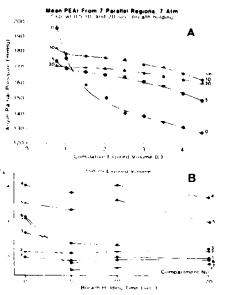
SUSTAINED MILITARY OPERATIONS AT MODERATE ALTITUDE: EFFECTS ON AEROBIC (AP) AND ANAEROBIC PERFORMANCE (ANP).
A.C. HACKNEY*, D.L. KELLEHER, AND J.A. HODGDON*. Exercise Physiology Laboratory, UNC, Chapel Hill, NC 27599 and Naval Health Research Center, San Diego, CA 92138.

Sustained military operations (SMO) at altitude lead to degraded combat effectiveness. Earlier studies have demonstrated lower maximal and submaximal work capacities at altitude. This study evaluated the residual effect of SMO on AP and ANP of US Marines conducting mountain warfare training at altitude (2100 to 2900 m). Training consisted of rock climbing, foot marches (4.2 km/day, ~25kg pack load) and mountain warfare infantry maneuvers. AP and ANP were measured on 16 volunteer subjects by graded (30 W/min) cycle ergometry and 30 sec Wingate protocol, respectively. Measurements were made at sea level (SL) prior to departing, 12 hours prior to commencing a 5 day infantry exercise at altitude (AL1), and immediately following the exercise (AL2). Subjects had been training at altitude for 11 days prior to AL1. Altitude (AL1 and AL2) significantly elevated (6% and 12%, respectively) absolute oxygen consumption (VO2) for all workloads greater than 150 W (AL1 vs AL2, N.S.). Altitude did not alter ANP (SL vs AL1, N.S.). However, sustained military operations (AL1 vs AL2) significantly reduced absolute ANP (695±29 W vs. 645±31 W) and relative ANP (9.1g±0.2 W/kg vs. 8.6g±0.3 W/kg); all values mean±S.E.M. These findings indicate a differential effect of sustained military operations at altitude on AP and ANP. Supported by Naval Medical Research and Development Command Work Unit M0096.002.

74.4

SLOW DIFFUSION WITHIN COMPARTMENTS AT 7 ATMOSPHERES.
Julio C. Cruz. Dept. of Anesthesiology & Physiology Medical College of Ohio, Toledo, Ohio 43699.

The hypothetical 7-compartment lung model, with parallel and series components, that was used to congruently describe experimental data of expired partial pressures of argon obtained at 1 atmosphere (ATA) (Cruz, Physiologist 31:A169, 1988), did not describe experimental data (symbols of fig. A) obtained at 7 ATA. However, a modification of the series component allowed to describe congruently the data at 7ATA (continuous lines of fig.A).The faster mixing observed at 7 ATA than at 1 ATA (Cruz, IUPS, 1989) appears to be due to convection-diffusion effect (no breath holding maneuver). However, when the breath is held in inspiration for 5, 10, or 20 sec. before expiring, no significant changes in argon fraction (F_{Ar}) is observed in 5 of the 7 compartments (fig B), which is at variance with 1 ATA (See figure of Cruz, FASEB 3:A686 1989). It is concluded slow mixing takes place by diffusion within compartments.



74.5

DIFFERENTIAL EFFECTS OF HYPERBARIC HYPEROXIA ON ULTRASTRUCTURE OF MITOCHONDRIA IN GLOMUS CELLS AND NERVE ENDINGS IN THE RAT. A.K. Sherpa* , D. Torbati, A. Mokashi*, K.H. Albertine, and S. Lahiri. Univ. of Penn. Sch. of Med., Philadelphia, PA. 19104-6085

Because mitochondrial oxidative metabolism, glomus cell and the innervation of glomus cells have been implicated in oxygen chemosensing, and because chronic hyperoxia attenuates oxygen chemosensing, we studied ultrastructure of mitochondria in glomus cells and its sensory nerve in the cat that were exposed to hyperbaric hyperoxia (99% O_2 at 5 ATA) for 90 to 135 minutes. The carotid bodies were fixed in situ by perfusion with buffered gluteraldehyde and paraformaldehyde, and prepared for electron microscopy and morphometry. We found that the glomus cell mitochondrial cristae (intermembrane space) was significantly reduced from (mean ± S.D) 0.031 ± 0.05 um to 0.019 ± 0.05 um in HBO exposed cats. The density of mitochondria in glomus cells increased from 13.09 ± 0.62 % of the cytoplasmic volume in the control to 17.47 ± 0.49 % in HBO cats. Volume density of the nerve ending mitochondria (15.22 ± 6.54 % control vs 13.77 ± 4.61 % HBO) did not change significantly. The selective effect of hyperoxia on glomus cell suggests that it is an important site of oxygen chemosensing. (Supported in part by HL-19737-12 and HL-07027-14)

74.6

TIME-OF-DAY ORIENTATION IS IMPORTANT IN TIMING AND LEVEL OF PHYSIOLOGIC VALUES. **L. Farr, C. Todero*, A. Keene*, G. Erickson* & R. Osborne*. College of Nursing, Univ. of Nebraska Med. Cntr., Omaha, NE 68105.**

Morningness/Eveningness has been reported to be a factor in the timing of temperature and heart rate circadian rhythms. The purpose of this study was to compare the timing and mean levels of these and other physiological variables in morning and evening individuals. Fifty-five healthy volunteers between the ages of 19 and 55 were divided into morning, evening and neither chronotypes using the Morningness-Eveningness Questionnaire (Horne & Ostberg, 1976). Subjects measured their temperature, heart rate, systolic and diastolic blood pressures, grip strength and peak expiratory flow every two hours from 0600 to 2200 hours for four consecutive days. Data were analyzed by cosine regression to determine the time of peak and rhythmic mean for each variable. Daily peaks of all variables were distributed according to time-of-day orientation with the greatest differences in systolic and diastolic blood pressures. Daily mean blood pressures were higher for morning than evening subjects. Neither-type subjects' timing and levels were intermediate. An inverse relationship was observed between heart rate and chronotype. Time-of-day orientation appears to be a factor in the distribution of physiological variables. Supported by DHHS # 1-R01 NU01098).

LUNG: GENERAL

75.1

EFFECT OF LARGE TIDAL VOLUME ON $\dot{V}_A/\dot{Q}$ INEQUALITY DURING PEEP IN THE DOG. K. Tsukimoto*, J. Arcos*, W. Schaffartzik*, P.D. Wagner and J.B. West. Department of Medicine, UCSD, La Jolla, CA 92093.

The occurrence of a high $\dot{V}_A/\dot{Q}$ mode during PEEP has been attributed to redistribution of pulmonary blood flow. In a previous study (FASEB J. 3:A686,1989), isocapnic hyperventilation appeared to reduce the high $\dot{V}_A/\dot{Q}$ mode and result in a unimodal distribution. But because we increased both inspired CO_2 and tidal volume (V_T) simultaneously, we could not conclude which of the two factors played the major role. We therefore compared two groups of anesthesized and passively hyperventilated dogs, one isocapnic with added CO_2 (n=4) and one without added CO_2 (n=4). After normal V_T baseline measurements with 5 cmH_2O PEEP, V_T was doubled in both groups. In the CO_2 group, $\dot{V}_A/\dot{Q}$ distribution was measured before and during CO_2 inhalation. Each $\dot{V}_A/\dot{Q}$ measurement was done after 60 min by multiple inert gas elimination. In both groups, a high $\dot{V}_A/\dot{Q}$ mode (10.5 ± 3.5% [mean ± SE] of ventilation in the CO_2 group, 11.8 ± 5.2% in control group) was seen at baseline, but decreased after 60 min (3.6 ± 2.8%, 2.0 ± 1.2%) and 120 min (0.0 ± 0.0%, 0.1 ± 0.1%) of large V_T without relation to CO_2. Large V_T seemed to diminish the high $\dot{V}_A/\dot{Q}$ mode over a period of time with an increase in alveolar dead space (estimated by the difference between inert gas dead space and Fowler's dead space), suggesting that the high $\dot{V}_A/\dot{Q}$ mode became alveolar dead space. A possible mechanism is that large V_T elevates alveolar pressure and may cause gradual compression of pulmonary capillaries in non-dependent high $\dot{V}_A/\dot{Q}$ regions. (Supported by NIH grant HL17731)

75.2

EFFECTS OF TEMPERATURE ON CAPILLARY CO_2 EXCHANGE. T.A. Heming & A. Bidani. Dept. Medicine, Univ. Texas Medical Branch, Galveston, TX 77570.

We investigated effects of temperature on kinetics of pH equilibration and HCO_3^- dehydration in isolated, saline-perfused rat lungs, and modulation of those effects by inhibition of pulmonary carbonic anhydrase (CA) with acetazolamide (ACTZ). Lungs were maintained and perfused with KRB solutions at 25-37°C. CO_2 excretion (μmol/min) and the magnitude of postcapillary $CO_2/HCO_3^-/H^+$ disequilibria (ΔpH) were measured. Total CO_2 efflux (μmol/min torr) was partitioned into that attributable to dissolved CO_2, uncatalyzed HCO_3^- dehydration and catalyzed HCO_3^- dehydration. Half-time for $CO_2/HCO_3^-/H^+$ equilibration increased ~3-fold from 37 to 25°C and, as a consequence, the observed post-capillary ΔpH doubled at 25°C. Temperature had little effect on total uncatalyzed CO_2 efflux (contribution of dissolved CO_2 + uncatalyzed HCO_3^- dehydration); decreases in the uncatalyzed HCO_3^- dehydration rate at lower temperatures were offset by increases in perfusate CO_2 solubility. Catalyzed CO_2 efflux (contribution of catalyzed HCO_3^- dehydration) increased with temperature. An Arrhenius plot of catalyzed efflux versus temperature yielded a CA I-like activation energy. Dixon plots of catalyzed efflux versus ACTZ concentration yielded K_I~1-2 μM, in agreement with previous calculations for rat lung CA and consistent with the CA I-likeness of the lung enzyme. These studies further characterize the lung tissue CA-catalyzed/facilitated efflux of CO_2.

75.3

PULMONARY GAS EXCHANGE AFTER CARDIAC SURGERY: THE EFFECTS OF DIFFERENT MODES OF VENTILATION. M.D. Hammond, D. Valentine*, J.B. Downs*, N. Sears* and W.R. Sims. Departments of Anesthesiology, Medicine and Surgery, U. South Florida College of Medicine, Tampa, FL 33612.

Moderate ventilation-perfusion inequality and right to left shunting are commonly seen during mechanical ventilation following cardio-pulmonary bypass. We used the multiple inert gas elimination technique to study the effects of 3 modes of ventilation [Volume Control (CMV), Pressure Support (PSV) and a new mode, Airway Pressure Release Ventilation (APRV)] on gas exchange in 5 patients following cardiac surgery. Settings on each mode were adjusted to produce equivalent mean airway pressures and arterial O2 and CO2 tensions. Heart and respiratory rates, expired ventilation, airway, pleural and systemic & arterial vascular pressures were continuously recorded. RESULTS: Respiratory gas tensions were similar on all modes at constant FIO2. The $\dot{V}_A/\dot{Q}$ distribution was also similar, with a slight reduction in deadspace on APRV versus CMV:

	logSDQ	logSDV	shunt%	deadspace%
CMV	0.98±0.4	0.64±0.1	16.0±8.0	36.0±7.0 *
PSV	1.12±0.5	0.72±0.3	20.0±10.0	38.0±10.0
APRV	1.08±0.6	0.67±0.2	22.0±10.0	30.0±6.0 *

(MEAN ± SD, * = P < 0.05)

CONCLUSION: These data indicate that the $\dot{V}_A/\dot{Q}$ distribution is relatively insensitive to the mode of mechanical ventilation when mean airway and vascular pressures are constant.

75.4

POSTURE DEPENDENCE OF GAS EXCHANGE IN ANESTHETIZED DOGS. K.C. Beck, J. Vettermann and K. Rehder. Mayo Clinic and Foundation, Rochester, MN, 55905

The mean alveolar-arterial oxygen partial pressure difference is significantly larger during mechanical ventilation with 40% oxygen in anesthetized dogs studied supine compared to prone (J. Appl. Physiol. 64:1864, 1988). To determine if the impaired oxygenation in the supine position is due to increased right to left shunt or increased mismatching of ventilation to perfusion ($\dot{V}_A/\dot{Q}$), we used the inert gas elimination technique to study 9 dogs in supine and prone positions while anesthetized, paralyzed, and mechanically ventilated with room air. With tidal volume and breathing frequency kept constant, arterial carbon dioxide ($PaCO_2$) was unchanged by position. Mean supine-prone differences were (± SD, N=9; * = P<0.05)

Δ $\dot{Q}$, l/min	-0.8 ± 1.6	Δ $\dot{Q}_S/\dot{Q}$, %	0.8 ± 1.1
Δ PaO_2, mmHg	-11.0 ± 6.9*	Δ V_D/V_T, %	1.7 ± 3.7
Δ (A-a)DO_2, mmHg	11.1 ± 4.7*	Δ lnSD $\dot{Q}$	0.3 ± 0.2*
Δ Ven admix, %	3.0 ± 3.1*	Δ lnSD $\dot{V}$	-0.2 ± 0.6

We conclude that the difference in oxygenation between the prone and supine positions is due to a difference in $\dot{V}_A/\dot{Q}$ matching, presumably because of changes in vertical distributions of ventilation and/or perfusion. (Supported by HL-30937 and HL-21584).

75.5

DISPLAY OF THE ALVEOLAR PLATEAU OF SINGLE-BREATH TESTS IN "DILUTION INDEX" FORMAT. Hugh D. Van Liew and Raj K. Mahajan*. Department of Physiology, School of Medicine, State University of New York at Buffalo, Buffalo, New York 14214, U.S.A.

In 1949, Fowler advocated calculation of a "dilution index" from the alveolar plateau of single-breath tests; the calculation provides an estimate of the dilution of resident gas in the lung that gave rise to the observed concentration. We illustrate the principle with vital-capacity breaths of a mixture which contains a low concentration of neon. The dilution was about three to one in young subjects (20 to 30 yrs), as if a vital capacity of 6 liters were mixed with a residual volume of 2 liters. The dilution was less, two to one, in older subjects (56 years), and tended to become as low as one to one during emptying of the closing volume. Description of single-breath results in terms of the dilution index allows common-sense interpretation of the level of the alveolar plateau, as well as its slope. Also, the dilution-index format allows comparisons of single-breath tests done by various methods: vital capacity inhalations of foreign gas as in our experiments, vital capacity inhalations of O_2 as in conventional tests, or breaths in which less than vital capacity volumes of marker gas are inhaled.

75.6

EFFECTS OF BODY POSITION AND END EXPIRATORY PRESSURE ON GAS EXCHANGE IN NORMAL DOGS. SM Yamashiro, ER Swenson, ME Middaugh*, and MP Hlastala. Seattle VA Medical Center and University of Washington, Seattle, WA 98108

Five anesthetized and mechanically ventilated dogs breathing air were studied prone and supine and in the prone position with 10 cm H_2O positive end expiratory pressure (PEEP) and -10 cm H_2O negative end expiratory pressure (NEEP). Standard respiratory gas exchange, hemodynamics and V_A/Q distributions by the multiple inert gas elimination technique (MIGET) were measured 30 minutes after each change in position or end expiratory pressure. At constant minute ventilation, CO_2 production and O_2 uptake; arterial PO_2 was 9.8 torr higher ($p < 0.05$) in the prone than in the supine position and MIGET derived indices of V_A/Q mismatch showed 30% less heterogeneity ($p < 0.05$). NEEP decreased inert gas dead space ventilation, V_{Dig}/V_T by 16% ($p < 0.05$) and increased V_A/Q mismatch by 38% ($p < 0.05$) and PEEP increased V_A/Q mismatch by 140% ($p < 0.01$) in comparison to zero end expiratory pressure. With NEEP, arterial PO_2 and PCO_2 did not change significantly reflecting the opposing effects of V_A/Q mismatch and reduced V_{Dig}/V_T on arterial blood gases. With PEEP, PaO_2 fell 7 torr ($p < 0.05$) and $PaCO_2$ rose 7 torr ($p < 0.05$). We conclude that 1) V_A/Q mismatch is less and gas exchange is superior in the prone position than in the supine position and 2) NEEP causes less gas exchange impairment than PEEP since V_A/Q mismatch is less and V_{Dig}/V_T falls.

75.7

ARTERIAL OXYGEN DESATURATION DURING HEAD-OUT WATER IMMERSION.
Toniann Derion*, Harold J.B. Guy*, Walter Schaffartzik*. (SPON: G. K. Prisk). Dept. of Medicine S-031, UCSD, La Jolla, CA, 92093.

The hydrostatic counterpressure and resultant central hypervolemia occurring during immersion are associated with a functional impairment in pulmonary gas exchange and arterial oxygenation. We studied lung volume changes and the time course of arterial oxygen desaturation in 4 normal males, age 38 ± 4 yrs (mean ± SEM), during 20 min of thermoneutral, seated, head-out immersion (HOI). Saturation (SaO_2) fell from the initial HOI value of 98.8 ± 1.0% to a minimum value of 92.0 ± 2.1% after 2 min ($p<0.05$). Recovery followed: 94.8 ± 1.5% at 5 min; 96.3 ± 2.1% at 10 min; 96.8 ± 1.5% at 15 min; 97.0 ± 1.4% at 20 min. All recovery values were significantly less ($p<0.05$) than the initial value. During HOI, expiratory reserve volume (ERV) decreased (68.3%) to 0.64 ± 0.13 L from the dry control value of 2.02 ± 0.55 L ($p=0.05$) and was not significantly different from the closing volume, 0.99 ± 0.13 L ($p=0.1$). At 20 min, PaO_2 was 74.3 ± 4.0 mmHg and $PaCO_2$ was 39.3 ± 2.5 mmHg. The acute hypoxemia observed suggests a maldistribution of ventilation which may be attributed to the decreased ERV. (Supported by NASA NAGW-897.)

75.8

EFFECT OF THE MECHANICAL ACTION OF THE HEART ON INTRAPULMONARY GAS MIXING IN DOG LUNGS. J. Piiper, E. Calzia* and M. Meyer*. Department of Physiology, Max Planck Institute f. Exp. Medicine, D-3400 Göttingen, F.R.G.

A technique of experimentally induced reversible myocardial arrest in intact closed-chest dogs was used to assess the significance of the mechanical action of the heart for intrapulmonary gas mixing (cardiogenic mixing). Cardiac arrest of about 20 s was repeatedly (8-15 times) induced by intracoronary injection of acetylcholine (35 mg) during which periods series dead space (V_D) and slope of the alveolar plateau (S) of He and SF_6 were determined by constant-flow single-breath washout technique. The measurements were performed in 7 anesthetized mechanically ventilated dogs (mean body wt 22 kg) and the effects attributable to the action of the heart were obtained with reference to control conditions, i.e. with the heart beating. The heart arrest/control ratio of V_D, 0.95±0.05 for He and 0.94±0.07 for SF_6 (means±SD), was not significantly different from unity ($p>0.05$) and the similar ratios of S, 1.03±0.10 (He) and 1.05±0.14 (SF_6) revealed no detectable effects ($p>0.05$) attributable to the myocardial contraction. It is concluded that in intact anesthetized mechanically ventilated dogs the action of the heart does not enhance intrapulmonary gas mixing.

Supported by the Deutsche Forschungsgemeinschaft, SFB 330, Göttingen.

75.9

MECHANISM OF HELIUM-SF_6 CROSSOVER DURING MULTIPLE BREATH WASHOUTS. G. Berdine and J. Lehr* Univ Tex Hlth Sci Ctr and Audie L. Murphy VA Hospital, San Antonio, TX 78284, and Harvard School Pub Hlth, Boston, MA 02115.

Both parallel and serial mechanisms have been proposed to explain why He and SF_6 concentration curves cross under certain conditions during multiple breath washouts of mammalian lungs. To further study He-SF_6 crossover, we simulated the convection-diffusion equation in a single trumpet human lung model which included mixing in large airways, and performed washout studies in six exsanguinated 20 kg juvenile pigs and five exsanguinated adult dogs. The model simulations predicted He-SF_6 crossover for a tidal volume (V_T) of 5 ml/kg, but not 10 ml/kg, and coincided with significant stratified inhomogeneity. None of the pigs demonstrated crossover for 10 and 20 ml/kg washouts, and only two demonstrated crossover at 5 ml/kg. One of the dogs demonstrated crossover at 20 ml/kg and all demonstrated crossover at 5 and 10 ml/kg. He-SF_6 crossover occurs in dogs at physiologic V_T despite their extensive collateral ventilation. Our studies suggest that the unusually large central airways of the dog may promote stratified inhomogeneity, and thus He-SF_6 crossover. We believe these findings support stratified, rather than parallel, inhomogeneity as the explanation for He-SF6 crossover in mammals. Supported by NHLBI HL-32674 and HL-33009.

75.10

UPPER AIRWAY DISTENSIBILITY AND COLLAPSIBILITY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA JW Shepard, Jr, M Garrison*, W Vas*, Mayo Clinic, Rochester, MN 55905 and VA Medical Center, St. Louis, MO 63125

The present study was performed to evaluate the distensibility and collapsibility characteristics of regional segments of the upper airway (UA) in patients with obstructive sleep apnea (OSA) and normal subjects in response to changes in airway pressure. Seventeen male patients with moderately severe OSA and 13 normal subjects underwent computerized tomography (CT) of the UA in the supine position while awake. Axial views were obtained from the level of the hard palate to the hypopharynx under conditions of -5, 0, and +10 cm H_2O of continuous airway pressure (CAP). The results indicated that minimum UA cross-sectional area (A_{min}) occurred within 20 mm of the hard palate in the retropalatal region of the UA in 16/17 (94%) of the patients and 12/13 (92%) of the normal subjects. Continuous negative airway pressure (CNAP = -5 cm H_2O) failed to significantly decrease either A_{min} or mean UA cross-sectional area (A_{mean}) in either the patients or normal subjects indicating good UA load compensation during wakefulness. Continuous positive airway pressure (CPAP = 10 cm H_2O) significantly increased A_{min} and A_{mean} to a similar extent in both groups indicating good UA distensibility. Minimal UA cross-sectional area was significantly smaller by 40%, 33%, and 37% in the patients with OSA compared to the normal subjects at -5, 0, 10 cm H_2O of CAP, respectively. In contrast, A_{mean} did not differ between groups. The CT scan criteria of A_{min} less than or greater than 1.0 cm^2 during ventilation at atmospheric pressure correctly categorized patients with OSA and normal subjects with an accuracy of 70%. The behavior of the UA in response to nasal CPAP and CNAP failed to increase the accuracy of CT scan criteria for the diagnosis of OSA. (This work supported by the Mayo Clinic, Mayo Foundation, and Veterans Administration.)

75.11

COMPARISON OF RETROGLOSSAL UPPER AIRWAY (UA) DYNAMICS AND GENIOGLOSSAL ELECTROMYOGRAPHIC (EMGgg) ACTIVITY IN NORMAL YOUNG MALES CD Burger,AW Stanson, PF Sheedy, PR Westbrook, JW Shepard, Jr, Mayo Clinic, Rochester, MN 55905

The retroglossal (extending from below the soft palate to the tip of the epiglottis) UA in 10 subjects was evaluated with a rapid CT scanner. CT scans and EMGgg were obtained during wakefulness and under the following conditions: FRC, end-inspiration during tidal breathing (VTei), RV, TLC during nasal breathing, and FRC at -10, -50, +10, and +50 cm H2O. Mean (Amean) and minimal (Amin) cross-sectional area (mm^2) of the UA and EMGgg activity are tabulated below (P values are vs. FRC). In the awake resting state there was little phasic EMGgg activity with tidal breathing. Exhalation to RV produced no significant change in UA size or EMGgg and inhalation to TLC resulted in large increases in UA size with a small but significant increase in EMGgg. At constant lung volume (FRC), the generation of negative pressure failed to decrease UA size and was associated with substantial increases in EMGgg. In contrast, positive pressure resulted in a large increase in UA size and EMGgg. While the increased in EMGgg in response to negative pressure can be interpreted as appropriate load compensation, the significance of increased EMGgg with positive pressure is unclear. This response during wakefulness is the opposite of the decrease in EMGgg observed with the appplication of positive pressure (CPAP) during sleep.

CONDITION	Amean ± SE	P Value	Amin ± SE	P Value	EMGgg(mm) ± SE	P Value
FRC -50	156 ± 42	.142	116 ± 32	.417	14.1 ± 2.3	.0001
FRC -10	133 ± 36	.889	91 ± 31	.980	6.5 ± 1.4	.0013
FRC Nasal	133 ± 17		106 ± 14		4.1 ± 0.6	
FRC 10	329 ± 46	.0001	292 ± 44	.0001	7.9 ± 1.3	.0001
FRC 50	441 ± 50	.0001	390 ± 51	.0001	13.1 ± 2.9	.0001
TLC	307 ± 64	.0005	250 ± 58	.0006	4.7 ± 0.7	.02
VTei Nasal	157 ± 21	.157	148 ± 23	.003	4.2 ± 0.6	.35
RV	157 ± 32	.221	118 ± 21	.203	3.9 ± 1.2	.62

75.12

Quantitation of Pharyngeal Soft Tissue Edema and Fat Using Localized Hydrogen MR Spectroscopy

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Soft tissue edema and/or fat infiltrating the upper airway may contribute to the pathogenesis of obstructive sleep apnea syndrome (OSAS). Sensitive, noninvasive methods for detecting and quantifying such pathologic processes do not exist. Hydrogen Ultrathin Phase-Encoded Spectroscopy (HUPSPEC), a new clinical spectroscopy pulse program developed at the Hosp. of the Univ. of PA., can measure relative quantities of water and fat with high spatial resolution within a line volume on standard 1.5 Tesla magnetic resonance (MR) images. Spatial and spectroscopic information are encoded along orthogonal axes. Preliminary phantom studies indicate that the relative intensities of fat and water correlate with their respective quantities down to 5% fat. Line volumes as small as 3mm wide and 3mm thick can be sampled. Our protocol measures pharyngeal soft tissue fat and water from the soft palate, lateral and posterior pharyngeal walls using two line volumes at the level of the soft palate. Magnitude spectra include regions of CSF and subcutaneous fat, serving as internal standards for water and fat. Well-resolved water and fat peaks are obtained from these regions. This combined use of MR imaging and proton spectroscopy promise to be a powerful tool in studying mechanostructural properties of the pharynx in OSAS.

75.13

Role of Head Tilt on Airway Patency: An MRI Based Analysis

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To evaluate the role of head tilt on airway patency we have volumetrically scanned, via multi sliced spin echo magnetic resonance imaging, a human volunteer with neck extended, neutral, and flexed. Oblique sections were selected from the volumetric image, perpendicular to the local airway long axis at the: 1) retro-palatal; 2) retroglossal, and 3) retro-epiglottal regions. In region 1, cross sectional area decreases from extension to flexion with A-P dimensions remaining essentially unchanged and lateral wall "thickening." Movement of lateral fat pads centrally suggest a potentially important role of lateral neck flexors in reducing airway area. In region 2 the major change was also in lateral dimension. In region 3, not only do the lateral walls fold inwards, but the epiglottis is forced back towards the posterior wall and the valeculae is obliterated. Volumetric analysis showed an elongation of the retroglossal oropharynx and a long axis compression yet increased cross sectional area of the hypopharynx with neck flexion. A reduced volume in the retropalatal region appears to be accompanied by a bellowing of posterior nasopharynx. Many of these features of neck flexion are features which occur in sleep apneics in the neutral position.

EAH is an EI of the AHA. Supported in part by HL R01-42672 and P50-42236

75.14

INFUSION OF ADENOSINE OR DIPYRIDAMOLE IMPROVES THE DISORDERED BREATHING DURING SLEEP IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA. L. Findley, R. Wesley*, and L. Belardinelli* University of Virginia

At present there is no good pharmacologic treatment of obstructive sleep apnea (OSA). The nucleoside adenosine (ADO) has been shown to stimulate breathing by increasing awake ventilatory drive in normal subjects. Nucleoside uptake blockers such as dipyridamole (DPM) increase the extracellular levels of ADO. This study examined the efficacy of ADO and DPM in improving the disordered breathing during sleep in patients with OSA. During sleep, intravenous ADO (50-75 mcg/kg/min, N-4) or DMP (80mcg/kg/min, N-4) was administered over 5 minutes. Three patients given DPM were subsequently given the ADO antagonist, aminophylline (AM)(3 mg/kg).

APNEA TIME (SEC)/5 MINUTES OF SLEEP

CONTROL	98±23	CONTROL	113±36	MEAN±SE
ADO	*49±21	DPM	* 57±44	*P<0.05
POST DRUG	96±30	AM	89±37	

The mean oxyhemoglobin saturation significantly increased during both ADO and DPM infusions, and the number of apneas/5min was significantly lower during ADO infusion. We conclude that ADO improved the disordered breathing during sleep in patients with OSA. ADO, ADO analogs, and nucleoside uptake blockers may represent important new therapies.

75.15

ATTITUDE TOWARD SMOKING IN MEDICAL STUDENTS. **M.F. Petrini, J.K. Mansel, I. Freeman*, J.M. Mahan*, and J.R. Norman Univ. MS Med Ctr. Jackson MS 39216**

Since physician's advice can be an important impetus to smoking cessation, we surveyed 80 1st year (M1) and 60 2nd year (M2) medical students to determine their attitude toward smoking. Ten percent of M1's but only 1 M2 admitted to smoking; 16% of M1's and 30% of M2's were ex-smokers. Approximately 70% considered the risks of smoking very important with respect of their personal smoking decision, yet nearly 60% of the non-smokers thought that factors such as peer fellowship or release of tension may cause them to start; 83% of M1's and 95% of M2's believed that they won't be smoking by the end of their residency. Less than 5% thought that quitting was easy, less than 50% thought it hard, but possible with will power alone. Slightly less than 40% in both groups believed that the percentage of adult smokers in this country is between 25 and 35%. Approximately 75% of smoking and non-smoking M1's believed that physicians should volunteer information about the health effect of smoking to their patients; only 28% of M2's held the same belief. Among M1's, 71% believed that between 5 and 10% of smokers would quit if their physician provided them with information, but only 50% of M2's thought physicians to be that effective.

75.16

DIRECTED GRAPH METHOD FOR ENCODING ALVEOLAR SEPTAL GEOMETRY. **W. DeVries* and D.H. Eidelman, Meakins-Christie Laboratories, McGill University, Montreal, Quebec, H2X 2P2, Canada.**

Lung parenchyma is a complex three dimensional arrangement of alveoli and alveolar ducts. Morphometric study of parenchymal structure is usually carried out manually using light microscopic sections to measure average alveolar size. Information regarding the organization and interconnectedness of alveolar walls would aid in the understanding of the pathophysiology of diseases such as emphysema, in which the regional distribution of destruction is likely to be important. The tedious nature of manual methods has made it difficult to obtain this information. We therefore wished to develop a method to permit automated measurement of parenchymal structure by computer. This requires an internal representation of the image which records its geometric arrangement. For microscopic sections of pulmonary parenchyma, a directed graph is an attractive method. We studied 512 X 512 binary images of standard microscopic sections of human lung parenchyma, magnification 63X. After thinning the image, we generated directed graphs on a pixel by pixel basis. Resulting images showed minor deviations from the original, and largely preserved the geometric relationships between alveolar walls. This method should permit automatic analysis of pulmonary parenchymal geometry. (Supported by the Banting Foundation and the Quebec Thoracic Society)

75.17

GLUCOCORTICOIDS INCREASE EXPRESSION OF NEUTRAL ENDOPEPTIDASE IN TRANSFORMED HUMAN TRACHEAL EPITHELIAL CELLS. D.B. Borson, S. Jew*, D.C. Gruenert.* CVRI, Dept Physiol UCSF, San Francisco, 94143.

Neutral endopeptidase (NEP) is a membrane-bound peptidase present in several different cell types in the airways. Previous studies have shown that NEP modulates the actions of a variety of biologically active peptides on several airway functions. Recently, we have demonstrated that reductions in NEP activity in airway diseases is associated with increased responses to exogenous and endogenously released peptides. To determine what factors regulate the expression of NEP, we studied human airway epithelial cells transformed in vitro with an origin-defective SV40 plasmid. We measured enzymatic activity using [^{3}H-Tyr, D-Ala^2]-leucine enkephalin, and found that activity increased with cell density (1.4 ng/10^6 cells at 530 cells/cm^2 and 15.5 ng/10^6 cells at confluency, 646 X 10^3 cells/cm^2). In both confluent and non-confluent cultures, the glucocorticoid budesonide increased NEP activity in time-and concentration-dependent fashions, with maximal effects of approximately 10 ng/10^6 cells greater than control observed after 6 days incubation and at 10^{-7}M. Transcription was assessed by Northern blot analysis of total cellular RNA. Blots were hybridized in the presence of formamide and washed at high stringency. In the absence of budesonide, a prominent band was found corresponding to 3.5 kb. Increasing concentrations of budesonide increased the intensity of the 3.5 kb band and caused the appearance of an additional band at 6.5 kb. The 6.5 kb band also increased in intensity with increasing concentration. We conclude that NEP expression is regulated by two mechanisms, one dependent on cell growth or density, and another dependent on glucocorticoids, and that the increased levels of enzymatic activity in steroid-treated cells is due to increased NEP gene transcription. (Supported by HL-24136, HL-38947, and DK-39619).

75.18

COMPARISON OF THE RESPONSES OF AN ISOLATED INNERVATED GUINEA PIG TRACHEAL PREPARATION TO INTRATRACHEALLY VS. EXTRATRACHEALLY ADMINISTERED VASOACTIVE INTESTINAL PEPTIDE (VIP). **T. Takubo*, K. Banks* and J.G. Martin. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, H2X 2P2, Canada.**

The purpose of the study was to evaluate the importance of the epithelium in determing the potency of exogenous VIP in inhibiting responses of isolated guinea pig trachea to vagal stimulation. Isolated innervated tracheal tubes (n=40) were mounted in glass organ baths in Krebs-Henseleit solution at 37 C and gassed with 95% O_2 and 5% CO_2. The vagal nerve trunks were stimulated (20V, 1 msec, 10 sec) at low frequency (0.5 Hz) and high frequency (0.5 Hz) alternately. We compared the effects on intratracheal pressures of VIP (10^{-4} to 10^{-7}M) administered to the inside or outside of the trachea, with and without phosphoramidon ($5*10^{-6}$M), and with and without intact epithelium. VIP inhibited responses to both high and low frequency stimulation. There was a significant difference between VIP administered to the inside and outside ($p<0.001$). Removal of the epithelium almost abolished this difference. Phosphoramidon potentiated the action of VIP. These data indicate that epithelium reduces the efficacy of VIP. We suggest that the epithelium is a diffusion barrier and may also be the site of degradation of VIP by endopeptidase. (Supported by M.R.C. Canada.)

75.19

MUCUS TRANSPORT IN A MINIATURIZED SIMULATED COUGH MACHINE: EFFECT OF CONSTRICTION AND SEROUS LAYER SIMULANT. M. King, M. Agarwal, J.B. Shukla, B.K. Rubin. Pulmonary Defense Group, University of Alberta, Edmonton, Canada

We investigated the transport of mucus gel simulant (MGS) in a constricted simulated cough machine (SCM), using blood plasma as a serous layer simulant (SLS). MGS was prepared from locust bean gum solutions crosslinked with varying amounts of added sodium tetraborate to produce gels of varying spinnability (8-20 mm, as tested in a filancemeter). In the original SCM (J Appl Physiol 1985; 58: 1776), the model trachea was a plexiglass channel of rectangular cross-section with the bottom surface lined with MGS. This was modified by replacing the upper flat surface with a surface containing a sinusoidal protrusion, which provided a flow convergence with minimum gaps of 6, 4 and 2 mm. Experiments for mucus transport were conducted for these minimum gaps, as well as for the non-convergent case (12 mm gap). MGS transport was determined as the minimum displacement of a line of marker dye placed in the MGS layer at the point of minimum convergent gap. It was shown that in all cases (dry as well as with SLS), MGS transport increased as the minimum constriction gap between the plane and the convergent top surface decreased. This increase was further enhanced if an SLS of lesser viscosity was used. It was also found that the transport of MGS increased as the depth of MGS layer increases or as the filance (spinnability) decreased in both non-constricted and constricted cases. The relationship between MGS transport and filance was maintained even in the presence of an SLS layer. Miniaturization of sample quantity was achieved by keeping the MGS layer depth constant (0.5 or 1 mm) but reducing the zone of loading from 13.4 cm to 1 cm, thus reducing the sample requirement to as little as 0.5 ml. This should facilitate the testing of sputum, since expectorates of 0.2 to 0.5 ml are readily obtainable from most patients with chronic hypersecretory disease. (Supported by Canadian Cystic Fibrosis Foundation)

75.20

SUBSTANCE P MODIFICATION OF PULMONARY EPITHELIAL BARRIER FUNCTION IN SPRAGUE DAWLEY RATS. E.M. App, G.T. De Sanctis, J.K. Trask, B.I. De Sanctis, J.E. Remmers, M. King. Pulmonary Defense Group, University of Alberta, Edmonton, Canada

Changes in pulmonary epithelial barrier function may reflect changes in transepithelial ion fluxes and/or changes in transcellular and/or paracellular water transport. Resorptive clearance has been found to increase in both acute and chronic airway inflammation. *In vitro* studies have demonstrated that neurokinins are able to influence ion fluxes and airway secretions in animal models, and peptidergic pathways have been implicated in the pathogenesis of asthma and cystic fibrosis. The results of previous studies fail to clearly delineate the underlying mechanisms and may not reflect the *in vivo* situation. SP is present in a subpopulation of primary C-afferent fibers which extend into the airway epithelium. Aside from its role in neurogenic inflammation, SP may play a physiological role in the maintenance of normal epithelial barrier function. In the present work we studied resorptive clearance following bolus administration of SP or vehicle into the lungs of rats. 11 healthy adult male Sprague Dawley rats were anesthetized and intubated on two occasions. Resorptive clearance (clr. in 1 hr) was measured using 99mTc labeled DTPA administered as a 100 µl /100 µCi bolus either in 0.9 % NaCl or 8.7 x 10^{-5}M SP (containing 11.7 µg SP) dissolved in 0.9 % NaCl. The results (mean±SD) are as follows:

Groups	# of rats	Clr in 1hr (%)	
Control	N: 11	71.5 ±20.1	
Substance P	N: 10	51.3 ±17.9	(p = .0037)

These results suggest that SP administration may reduce the rate of airway fluid resorption, i.e. increase airway barrier function. Given its known role as a neurotransmitter and its capacity to act as a secretogogue, it is possible that the decreased resorptive clearance is due to enhanced mucus discharge which could result in an augmented barrier. SP may , alternatively, have as yet undescribed intrinsic effects on epithelial function. These results (SP decreasing resorption) complement those described in our previous study of substance P depleted Fisher 344 rats (neonatal capsaicin treatment), where SP depletion increased resorption. This is consistent with the view that SP may have an intrinsic activity on the airway epithelium. (Supported by CCFF and MRC).

75.21

A NEW PLASTIC SUBSTRATE FOR ORGAN-CULTURE AND DIFFERENTIATION OF HUMAN LUNG. M.T. Hsu*[1], O.K. Reiss*[2], D. Ciurea*[3], and J. Gil[3]. [1]Dept. Microbiology and [3]Pathology, Mount Sinai Med. Ctr., New York, and [2]University of Colorado, Colorado.

A new type of plastic substrate was developed for culturing primary animal cells. This new substrate supported the growth and differentiation of human fetal lung in vitro. We noticed growth of a system of dichotomous branching tubes and expansion of alveolar sacs. Active transport was found inside the tubes. Electron microscopy revealed areas where epithelial lining consisted of tall cells with glycogen inclusions consistent with immature airways; peripheral areas showed differentiation of epithelium into squamous and cuboidal cells comparable to type I and II cells. The cuboidal cells contained many lamellar bodies of variable size and shape. Macrophages were present. Extracellular amorphous material with rare tubular myelin was seen lining the luminal spaces. Preliminary lipid studies show higher concentration of digestible Pi and low amounts of proteins, suggesting surfactant phosphalipid with little or no proteins.

75.22

LOWERING THE P_{O_2} OR COOLING INDUCES EPITHELIUM-DEPENDENT RELAXATIONS OF CANINE BRONCHI Yuansheng Cao and Paul M. Vanhoutte. Mayo Clinic and Mayo Foundation, Rochester, MN 55905

The present study was designed to investigate the effect of lowering the P_{O_2} or cooling on the modulatory role of the epithelium on the responsiveness of the underlying airway smooth muscle. Second order canine bronchial segments with or without epithelium were suspended and perfused intraluminally with modified Krebs-Ringer bicarbonate solution. The transluminal isometric tension was recorded. Experiments were performed during contractions to extraluminally administered-carbachol or potassium chloride. When lowering the P_{O_2} (from 600 mmHg to 140, 80, or 40 mmHg) or decreasing the temperature of the perfusion solution (from 37°C to 31, 29, or 27°C), the tissues with epithelium showed significantly larger relaxations than that without epithelium. The level of the epithelium-dependent relaxations were dependent on the partial pressure of oxygen or the temperature of the perfusion solution. The relaxations were not affected by indomethacin, methylene blue, or propranolol. In cascade superfusion experiments, epithelium-dependent relaxing factor could not be bioassayed. Those findings suggest that lowering the P_{O_2} or cooling can induce the epithelium to release a relaxing factor. The factor is neither a product of cyclooxygenase nor endothelium-derived relaxing factor. Furthermore, the factor probably is not released into the bronchial lumen, or if it is, it is catalyzed rapidly.

76.1

EFFECT OF AIRWAY SMOOTH MUSCLE RELAXATION IN PRETERM INFANTS WITH REACTIVE AIRWAY DISEASE.

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Reactive airway disease (RAD) in preterm infants consequent to mechanical ventilation and bronchopulmonary dysplasia (BPD) leads to changes in airway caliber. The associated dimensional deformation further alters airflow ($\dot{V}$) mechanics. Tracheal smooth muscle relaxation with β-2 agonist stimulation was studied in five preterm infants with BPD and RAD at term postconceptional age (BW:0.8±0.1, GA:26±2wk, and SW:1.8±0.3kg). Tidal volume (Vt,ml/kg), $\dot{V}$, driving pressure (P), P-V and $\dot{V}$-Vt were measured pre- and 1°, 3°, 6° post-albuterol(0.1/mg/kg) inhalation. Mean values of compliance (C,ml/cm$H_2$0/kg), pulmonary resistances (R,cm$H_2$0/L/S), resistive work (WOB,gm-cm/kg), and minute ventilation (ml/min/kg) were:

	Vt	C	Ri	Re	Rt	WOB	MV
Pre	6.3	0.46	96	148	104	37	440
Post 1°	8.2*	0.59*	38*	75*	57*	35	607*
Post 6°	7.0	0.62	48	89	62	26	526

Significant (*,p<0.05) reduction in Ri, Re, and Rt is associated with improved C, Vt, and MV. This study shows that the change in airway caliber with tracheal relaxation in RAD improves $\dot{V}$ mechanics.

76.2

EFFECT OF α-ADRENERGIC STIMULATION IN INFANTS WITH BRONCHOPULMONARY DYSPLASIA.

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Airway smooth muscle hyperplasia has been noted in infants with bronchopulmonary dysplasia (BPD). Brief, noninvasive, α-adrenergic stimulation was studied in mild BPD infants (breathing room air, at term postconceptional age). Seven infants (BW: 0.8±0.1kg, GA:26±2wks, SW:1.9±0.5kg) were studied pre- and 30 min. post-bronchoprovocation (ophthalmic phenylephrine HCL, 2.5% 1gtt q15minx3), and compared to placebo and to infants without BPD. Airflow ($\dot{V}$) and esophageal pressure (Pes/cm$H_2$0) were determined to calculate minute ventilation (MV,ml/min/kg), dynamic compliance (C,ml/cm$H_2$0), total pulmonary resistance (Rt,cm$H_2$0/L/s), resistive work (WOB,gm-cm/kg), and expiratory $\dot{V}$ ($\dot{V}$exp/L/min). Mean ±SEM values in BPD infants were:

	MV	C	Rt	WOB	Pes	$\dot{V}$exp
Pre	551±63	3.1±0.6	24±3	11±2	4.9±0.6	3±0.8
Post	508±82	2.0±0.4*	61±11*	23±5*	8.5±0.6*	2±0.4*

Significant (*,p<0.01) deleterious changes were observed as compared to placebo and normal infants. This study indicates even mild BPD is associated with reactive airway disease and α-adrenergic stimulation may induce bronchoprovocation.

76.3

DETERMINATION OF PULMONARY MECHANICAL FUNCTION IN INTUBATED NEONATES AND INFANTS FROM THEIR RESPONSE TO BRIEF FLOW PULSES.

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We have previously shown (ARRD 137:382, 1988) that pulmonary mechanical function may be evaluated from the response of the respiratory system to brief flow pulses. The short duration of each pulse suggests that this method may be suitable for uncooperative subjects such as neonates and infants. This approach was examined in 3 spontaneously breathing neonates suffering from infant respiratory distress syndrome (IRDS) and 2 infants suffering from chronic lung disease with evidence of bronchopulmonary displasia (BPD). The endotracheal tube was connected to a low impedance speaker enclosure modified to maintain the positive end-expiratory airway pressure (PEEP) equal to the PEEP level that was set on the ventilator. The speaker generated a free running train of pulses at 2 Hz. Impedance spectra derived from the pulse response of IRDS patients could be simulated with a simple RIC model. For these patients, compliance (0.36 ± 0.36 ml/cm H_2O) and resistance (125 ± 60 cm H_2O/l/s) derived from the impedance spectra and the estimates obtained using a conventional method formed fairly consistent ratios, being 0.46 ± 0.11 for compliance and 1.14 ± 0.14 for resistance. In contrast, the impedance characteristics for the BPD group were better approximated by including a shunt compliance, possibly reflecting the compliance of the central airways, to the RIC model. The differences in impedance between these two groups suggests that the pulse response may be used to identify changes in pulmonary mechanical function in neonates and newborns. (Supported by NHLBI Grant HL33274).

76.4

EXOGENOUS SURFACTANT(S) ADMINISTRATION BY CONVENTIONAL (CMV) AND HIGH FREQUENCY JET VENTILATION (HFJV).

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To determine if distribution of S is enhanced when administered by HFJV compared to CMV, 14 piglets (1.4 ± 0.3 kg, 1.3 ± 0.6 days old) were studied. Animals initially received CMV with FiO_2 = 1.0, maintaining $PaCO_2$ at 40 torr. S deficiency was induced by repeated saline lavage until PaO_2 < 100 torr and dynamic lung compliance (C_{RS} - computerized pulmonary function test) decreased > 50%. Three control animals were sacrificed and lung sections revealed diffuse, moderate atelectasis. Six animals received 100 mg/kg of S and 30 mins of CMV and 5 piglets received S and 30 mins of HFJV. S apoprotein was specifically labelled with technisium-99 and a gamma camera examined dynamic S distribution. S completely and symmetrically filled both lungs by 15 secs. There were no detectable differences between the CMV and HFJV groups over the 30 mins. Arterial/alveolar oxygen ratios (0.45 ± 0.03 pre, 0.09 ± 0.01 post-lavage, 0.36 ± 0.06 post-S; p < 0.001 ANOVA) and C_{RS} (1.7 ± 0.1 pre, 0.5 ± 0.1 post-lavage, 0.7 ± 0.1 mls/cm H_2O/kg post-S; p < 0.001) were not significantly different between the 2 experimental groups. Inflation patterns were significantly improved in both S treatment groups. Data suggests that S is rapidly and symmetrically distributed throughout the lung by both CMV and HFJV and causes significant improvement in oxygenation and lung inflation patterns.

76.51

A MULTI-CENTER RANDOMIZED TRIAL OF PRE-VENTILATORY VERSUS POST-VENTILATORY ADMINISTRATION OF SURFACTANT.

James W Kendig*, Linda Reubens*, Christopher Cox*, Herman Risemberg*, Albert Bartoletti*, Harry Dweck*, Robert H Notter*, Donald L Shapiro* (Spon: J.M. Davis). University of Rochester Medical Center, Department of Pediatrics (Neonatology) and SCOR for Respiratory Disorders of Newborns, Rochester, NY and Albany Medical Center and Westchester County Medical Center.

Very premature infants of 24-29 weeks gestation were randomized before birth to receive a 90 mg pre-ventilatory (Pre-V) dose of calf lung surfactant extract (CLSE) or a 90 mg post-ventilatory (Post-V) dose at several hours of age if FiO_2 was ≥ 0.40 and/or the MAP was ≥ 7.0 cm H_2O. Patients in both groups received additional doses of CLSE at 12 to 24 hour intervals if similar FiO_2 and MAP criteria were met. 479 patients were randomized in three centers (235 to Pre-V and 244 to Post-V). Pneumothorax (Pn-Thx) occurred in 6.8% of the Pre-V group and in 11.9% of the Post-V group (p=0.055 by Mantel-Haenszel [M-H]). The incidence of Pn-Thx in those infants ≤ 26 weeks gestation was 7.1% in the Pre-V group and 18.6% in the Post-V group (p=0.027 by M-H). The survival was 87.7% in the Pre-V group and 80.3% in the Post-V group (p=0.028 by M-H). The survival of infants ≤ 26 weeks was 75.3% in the Pre-V group and 54.2% in the Post-V group (p=0.006 by M-H). This trial demonstrates a significant advantage of using a Pre-V strategy to administer the first dose of CLSE in infants ≤ 26 weeks gestation.

76.6

EFFECTS OF XANTHINE ANALOGS ON RESPIRATION IN NEWBORN RATS.

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Methylxanthines (MX), such as theophylline, are commonly used in the treatment of recurrent apnea due to their stimulant effects on the respiratory center. Structure-activity studies have demonstrated that substitution of alkyl groups on the 3-position of the xanthine nucleus results in increased bronchodilator potency, while substitution on the 1-position is important for adenosine antagonism and CNS stimulation. Four different alkylxanthines were studied to determine the structural requirements for respiratory stimulation. Respiratory rates and volumes were determined in 4- to 7-day-old rats using a body plethysmograph. Measurements were made before and at 5 min intervals after s.c. injection of drug. Theophylline (1,3-diMX, 10-40 mg/kg) increased minute ventilation ($\dot{V}_E$) in a dose-related manner by as much as 45% over baseline. Increases were observed in both tidal volume (V_T) and respiratory rate (f). 1-MX (40 mg/kg) increased $\dot{V}_E$ by almost 20%, primarily by increasing f. Neither 3-MX (10-20 mg/kg) nor enprofylline (3-propylxanthine, 10-40 mg/kg) produced significant changes in $\dot{V}_E$. These data suggest that substitution at the 1-position of the xanthine nucleus is essential for respiratory stimulation. The effect may be further enhanced by substitution at the 3-position. The data further suggest that antagonism of adenosine receptors is necessary for alkylxanthine-induced respiratory stimulation. Supported by the American Lung Association and Pharmaceutical Manufacturers Association Foundation.

76.7

MORPHOMETRIC ANALYSIS OF THE VENTILATED IMMATURE LUNG: EFFECT OF MINIMIZING SURFACE TENSION. Kiran S. Deoras, Marla R. Wolfson, Jay S. Greenspan*, and Thomas H. Shaffer.Depts. of Physiol. and Peds. Temple Univ. Sch. of Med. and St. Christopher's Hospital for Children, Philadelphia, PA 19140.

To evaluate the histological effects of minimizing surface tension on the extremely immature lung, we analyzed sections of the lung obtained from lambs (105-115 dys gest. age) following 2-3 hrs of gas (GV) or liquid fluorocarbon (LV) ventilation . The ventilatory schema was adjusted according to lung mechanics and blood chemistry. Computerized image analysis was used to quantitate area (A), perimeter (P) and wall thickness (T) of the gas exchange spaces from standard histological sections. Parenchyma (Vp) and luminal regions (Vl) per unit area were quantitated densitometrically and the expansion index (I) was calculated as Vl/Vp. Lung sections from GV animals showed only minor areas of aeration with adjacent regions of atelectasis, air spaces containing diffuse proteinaceous exudate, hemorrhage, and hyaline membranes. In contrast, sections from LV animals showed clear and uniformly expanded gas exchange spaces. Morphometric analyses demonstrated that A, P, and I of the LV animals were significantly ($p < 0.05$) larger and T smaller as compared to the GV animals. These results demonstrate improved lung expansion and decreased lung injury in the LV animals. These findings indicate that reduction of surface tension by LV facilitates expansion of delicate lung parenchyma, supports gas exchange, and minimizes pulmonary barotrauma in the surfactant deficient immature animal. (HL 32031, AHA, BSRG RR 05417)

76.8

LARYNGEAL COOLING AND BREATHING PATTERN IN NEWBORN PUPPIES. O.P. Mathew, J.W. Anderson*, F.B. Sant'Ambrogio and G. Sant'Ambrogio. Depts. of Physiology and Pediatrics, University of Texas Medical Branch, Galveston, TX 77550.

Constant airflow through the upper airway in anesthetized newborn animals induces ventilatory depression. The role of laryngeal temperature in the above responses has not been studied. Experiments were performed in nine 1-5 day-old anesthetized puppies (from 3 litters) breathing through a tracheostomy. Tidal volume and laryngeal temperature were recorded while a constant stream of air (15-23 ml/s) at room temperature was passed in the expiratory direction for 20 s through the isolated upper airway. Warm (35-37°C), humidified air at the same flow served as control. When laryngeal temperature was decreased (-7.48 ± 0.92°C), a marked change in breathing pattern was observed (V_T 54.2 ± 4.7, T_I 186.6 ± 33.1, T_E 635.7 ± 179.2, V_T/T_I 44.6 ± 9.8% of control) Warm air at the same flow induced no significant changes (V_T 102.5 ± 2.1, T_I 100.5 ± 3.0, T_E 96.9 ± 3.0, V_T/T_I 103.4 ± 4.6% of control). Superior laryngeal nerve section abolished the effect of cooling on breathing pattern. We conclude that the depressant effect of airflow through the upper airway is entirely due to a decrease in temperature, possibly mediated by the stimulation of laryngeal cold receptors and/or inhibition of laryngeal mechanoreceptors. (NIH grants HL-20122 and HL-32921; J.W.A. is a Fellow of the Canadian Lung Association.)

76.9

EFFECT OF THEOPHYLLINE ON RESPIRATORY QUOTIENT (R) AND VENTILATORY RESPONSE TO HYPOXIA. H Porras* A Cote* A L Coates and M. Amies* McGill Univ. Montreal, Canada.

Theophylline (THEO), a drug frequently used in newborns, stimulates respiration but also increases metabolic rate. Since hypoxia influences both ventilation and metabolic rate in newborns, we non-invasively studied 4 piglets (age 6-7 days) in normoxia and 30 minutes after induction of hypoxia (PaO_2= 40 torr) during a control period (CONTROL) and after an infusion of THEO which achieved a blood level of 40 umol/L. All the studies were done in a quiet state, 2 days after instrumentation for blood gases sampling. O_2 consumption (VO_2) and CO_2 production (VCO_2) were measured in a metabolic chamber and alveolar ventilation (V_A) derived from VCO_2 and $PaCO_2$. In the CONTROL, V_A increased with hypoxia (18 + 4%) and R increased (0.82 + 0.03 to 0.91 + 0.01) due to a small decrease in VO_2, VCO_2 was either increased or unchanged. After THEO, there was no change in V_A and R in response to hypoxia, both VO_2 and VCO_2 been slightly decreased (R: 0.82 + 0.03 and 0.84 + 0.05). The normoxic values of V_A, VCO_2 and VO_2 where higher with THEO than in CONTROL ($p<0.01$). In conclusion, during CONTROL, hypoxia results in a shift towards increased carbohydrate utilisation with no change in metabolic rate. Under normoxic condition, exposure to THEO increases metabolic rate but does not change substrate utilisation. Subsequent exposure to hypoxia does not result in a change in substrate utilisation; the slight decrease in metabolic rate probably explain the lack of increase in V_A during hypoxia with THEO.

76.10

EMULATION OF PULMONARY SURFACTANT USING MIXTURES OF LIPIDS AND SYNTHETIC PEPTIDES MODELLED ON SURFACTANT PROTEIN (SP)B. R.Bruni*, A.Waring*, J.Amirkhanian*, W.Taeusch, King-Drew Med. Ctr. Dept. Pediatrics, Los Angeles, CA 90059

Synthesis of human SP-B (residues 1 to 25 and 49 to 66) was carried out by solid state peptide synthesis using the Merrifield method (UCLA Peptide Synthesis Facility). Sequences for synthesis based on computer analysis were selected that predicted amphipathic structures and probable sites of lipid interaction. These peptides (ca. 3%) were combined with lipid mixtures of dipalmitoyl phosphatidylcholine 68%, dioleyl phosphatidylglycerol 22%, palmitic acid 9%, (w:w). Peptide/lipid dispersions were assessed by surface fluorescent spectroscopy using endogenous tryptophan as the fluorescence emitter. Surface properties were assayed both on a Langmuir-Wilhelmy (L/W) balance and on a King- Clements (K/C) adsorption device. Selected mixtures were also tested in anesthetized rats made surfactant deficient by bronchoalveolar lavage. Negative controls were lipids without added peptide, and a positive control was surfactant TA, a bovine surfactant used clinically that contains native SP-B and SP-C. Fluorescent spectroscopy of lipid/peptides showed two emission peaks at 335 and 350 nm indicating that the peptides exist both at the aqueous lipid interface and in a lipid phase. The table shows means (+\-SD) for degree of surface compression (% of max) needed to achieve surface tensions < 10 mN/m (L/W); surface tension after 1 min adsorption (mN/m, K/C); and PaO2 in torr (for rats in 100% oxygen 30 min after treatment).

	PL	TA	B 1-25	B 49-66	B+B
L/W	0	58+/-2	49+/-2	23+/-2	39+/-2
K/C	71+/-1	44+/-1	58+/-4	58+/-4	53+/-2
PaO2	71+/-26	176+/-72	---	---	149+/-68

We conclude that synthetic SP-B's insert into lipids in aqueous dispersions; that synthetic SP-B's with lipids emulate biophysical characteristics of native surfactants; and that these mixtures can duplicate physiological effects of native surfactant in vivo.

76.11

CYCLIC RESPIRATORY MOTION IS NOT IMPORTANT TO MAINTAIN LUNG SURFACTANT PROPERTIES. Jesus Villar, Arthur S. Slutsky, Bruce Holm, Avi Nahum, Tom Corbridge, Ian Chin*, Paul Schumaker, J. Iasha Sznajder. Univ. of Toronto, Canada; Univ. of Chicago, IL.; Univ. of New York at Buffalo.

To examine the effect of cyclic lung stretch on surfactant function, we studied 8 healthy dogs ventilated with conventional mechanical ventilation (CMV) or constant flow ventilation (CFV), a technique in which normal blood gases are possible with no movement of the chest wall. The dogs were ventilated either with CMV or CFV for 4 or 8 hours. Thereafter, a bronchoalveolar lavage of the upper and lower lobes in each lung was performed, and samples were taken for surfactant and protein analysis. The results for the 4 and 8 hr studies were similar; the data presented are the means for both ventilation periods. PaO_2 on 40% O_2 was higher on CMV (190±21 mmHg) than CFV (151±41 mm Hg) [$p<0.001$]. All lavage samples reached a minimum surface tension of 15 mN/m. The lipid phosphorus concentration was similar in both groups (CMV:0.06±0.01 μM/ml;CFV:0.07±0.01μM/ml). The total protein concentration was not different on CFV (0.96±1.13 mg/ml) compared to CMV (0.54±0.24 mg/ml). The content of lysolipids was higher than normal but there were no significant differences between CFV and CMV (6.5±1.6% vs. 7.1±2.2%). We conclude that removal of cyclic lung stretch by CFV does not affect the surfactant composition of normal lungs.

77.1

T-LYMPHOCYTE RESPONSE TO EXERCISE TRAINING AND STRESS
Gerald D. Tharp and Tim L. Preuss* School of Biological Sciences, University of Nebraska, Lincoln, NE 68588

The impact of exercise training and stress on the immune response was examined by measuring the mitogenic response of spleen lymphocytes to the T cell mitogen concanavalin A. Male Sprague-Dawley rats were divided into four groups: Sedentary controls (N=11), Handled controls (N=12), Treadmill runners (N=10) and Voluntary runners (N=11) housed in running wheels. The Treadmill group ran at 22 M/min (0.8mph) for 45 min, 5 days per week for 8 weeks. After the training period spleen lymphocytes isolated from each rat were incubated with con A for 54 hours, pulsed with radiolabeled thymidine for 18 hours and counted for tritium activity. The mean cpm per group was: Sedentary-6839, Handled-8959, Voluntary runners-13126, Treadmill runners-18950. One-way ANOVA and Tukey's HSD test found the cpm of the Treadmill runners significantly different from the cpm of the Sedentary animals. These results indicate that the responsiveness of spleen lymphocytes to con A increases as the level of stress and exercise increases.

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77.2

EFFECTS OF COCAINE ON MUSCLE GLYCOGEN AND BLOOD LACTATE DURING EXERCISE.
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To determine the effects of cocaine on carbohydrate metabolism during steady state treadmill exercise, male rats were injected intravenously with cocaine-HCl (12.5 mg/Kg B.W.) or saline and then exercised (26 m/min, 10% grade) or rested for 30 min. Glycogen changes were measured in the soleus (SOL), red vastus lateralis (RVL), and white vastus lateralis (WVL) muscles, and lactate (LAC) concentration was measured in the blood. The data are shown in the Table below. (Values are $\bar{X}$ ± SE; glycogen = µmol/g; lactate = mM; n = 8-11; * = sig diff from saline; + = sig diff from rest, $P < 0.05$.)

	Rest		Exercise	
	Saline	Cocaine	Saline	Cocaine
SOL	21.6 ± 1.2	16.1 ± 1.2*	5.5 ± 0.5+	4.2 ± 0.4+
RVL	37.6 ± 2.8	35.9 ± 1.4	14.0 ± 2.2+	6.6 ± 1.1+
WVL	43.1 ± 1.2	38.2 ± 2.0*	30.9 ± 2.7+	16.2 ± 3.2*+
LAC	1.3 ± 0.07	1.6 ± 0.15	2.8 ± 0.2	5.8 ± 1.3*+

Cocaine appears to reduce glycogen in SOL and WVL at rest and to accelerate glycogenolysis in WVL and RVL during exercise. This latter effect, in addition to the elevated lactate levels in the cocaine group, could eventually reduce endurance capacity.

(Supported by NIDA Grant DA04382)

77.3

EFFECTS OF COCAINE ON BLOOD CATECHOLAMINE LEVELS IN EXERCISING RATS.
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Both cocaine and exercise are known to activate the sympathetic nervous system. The purpose of this study was to determine the additive effect of these two treatments on the levels of catecholamines (pg/ml) in the blood. Male rats were given an intravenous injection of either saline or cocaine-HCl (12.5 mg/Kg B.W.) and allowed to either rest or exercise (26 m/min, 10% grade) for 30 min. Blood samples were obtained within 45 sec of cessation of rest or exercise. The data ($\bar{X}$ ± SE) are shown in the table below: (D = Dopamine; E = Epinephrine; NE = Norepinephrine; n = 8-11 animals/group; * = sig diff from saline; + = sig diff from rest, $P < 0.05$.)

	Rest		Exercise	
	Saline	Cocaine	Saline	Cocaine
D	199 ± 8	1206 ± 37*	302 ± 22	1142 ± 68*
E	250 ± 21	577 ± 65*	770 ± 54+	2445 ± 133*+
NE	266 ± 34	594 ± 67*	372 ± 40	1500 ± 146*+

These data indicate a very marked additive effect of cocaine on E and NE during exercise, but not on D. Such high levels of E and/or NE during exercise may be indirectly responsible for the decreased endurance observed in a previous study (J.A.P. 64:884, 1988).

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77.4

TOTAL AND REGIONAL HINDLIMB MUSCLE FLOWS IN RATS FOLLOWING RIGOROUS ENDURANCE TRAINING.
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To determine the effects of rigorous endurance training on the flow capacity of skeletal muscle, total and regional pressure-flow relationships were determined in maximally vasodilated (papaverine) hindquarters of control (C) and endurance trained (ET) rats. ET rats were exercised on a motorized treadmill at 30 m/min (15% grade), 90 min/d, 5d/wk for 12 wks. The hindquarters were perfused with Tyrode's solution containing horse serum (20% v/v) and albumin (5 g/dl). Total flows determined at perfusion pressures between 30 and 55 mmHg were greater ($P \leq 0.01$) in ET compared to C, indicating an increased flow capacity in the ET hindquarters. Regional flows (radiolabeled microspheres) measured at 50 mmHg (mean±SEM, ml/min/100 g) to leg muscles composed of a variety of muscle fiber types are tabulated below:

Leg Muscle:	Soleus	Plan	G-red	G-mix	G-whi	EDL
C (n=10)	173±16	38±6	139±20	38±5	31±3	40±7
ET (n=10)	187±21	70±5*	182±16#	56±5*	34±4	50±8

* and # denote $P<0.05$ and $P<0.1$ compared to C, respectively.

These preliminary results suggest that this type of exercise training results in an increased flow capacity of hindlimb skeletal muscles, which appears to be associated primarily with oxidative, fast-twitch muscles. Supported by a grant from the College of Veterinary Medicine, University of Missouri-Columbia.

77.5

ANALYTICAL MODEL OF O_2 TRANSPORT AND UTILIZATION DURING MAXIMUM EXERCISE.
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A simple analytical model of pulmonary uptake, circulatory transport and peripheral utilization of a hypothetical "surrogate O_2" gas obeying Henry's law has been developed specifically to examine the complex interactions amongst these three components of the O_2 transport system. For such a gas, steady state pulmonary uptake in a (potentially) diffusion-limited single alveolus model was expressed as a monoexponential process, as was tissue O_2 transport out of the capillary (i.e. by an exponential equation for diffusion-limited O_2 movement). A third mass balance equation across the lungs permitted the writing of these three simultaneous equations in three unknowns (alveolar, arterial, and venous partial pressures). Input data required are inspired "O_2" concentration, alveolar ventilation, blood flow, blood "O_2 solubility" and both pulmonary and tissue diffusing capacities. At sea level, the model predicts that cardiac output is the most important quantitative determinant of $\dot{V}O_2max$, but at altitude, tissue diffusing capacity is more influential. The model also clearly identifies the way in which all input variables combine to set $\dot{V}O_2max$ (under the assumptions stated) in a well-integrated manner. While very simple, the model has value in making predictions about determinants of $\dot{V}O_2max$ and interactions amongst key variables that might be experimentally testable. (Supported by NIH grant HL 17731.)

77.6

EFFECT OF THE SITE OF SAMPLING IN THE MEASUREMENT OF FEMORAL VENOUS BLOOD GASES.
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To further investigate the role of tissue O_2 diffusion limitation of $\dot{V}O_2max$ in normal man, we adapted the continuous thermodilution technique to measure femoral venous bloodflow and to perform blood sampling during cycling exercise. Simultaneous blood samplings from a 7F catheter introduced 2 cm below the inguinal ligament and advanced 7 cm distally into the femoral vein (Dist) and from a 7F Swan-Ganz catheter placed in the same vessel and advanced 7 cm proximally (Prox), were carried out in 6 volunteers cycling 3 runs to maximal on one day (n=18) (F_IO_2: 0.21). Dist PO_2 was significantly lower than Prox PO_2 at rest (mean dif -5.7±1.2(SEM) torr, $p<0.001$) but no differences were shown at 60%$\dot{V}O_2max$ and at $\dot{V}O_2max$. A similar behaviour was shown in pH. In contrast, Dist PCO_2 was always slightly higher than Prox PCO_2 (1.2±0.4, $p=0.005$; 2.3±0.9, $p=0.025$ and 3.3±0.9, $p<0.002$). We conclude that the effect of bloodflow from the nonexercising areas on Prox O_2 and CO_2 is rather small at maximal exercise.

(DGE Gen Cat, CICYT PA86-0345, SEPAR/88).

77.7

DYNAMICS OF RESPIRATORY AND CARDIAC FUNCTION IN HEART TRANSPLANT RECIPIENTS DURING EXERCISE. M.Meyer**, C.Marconi*, B.Grassi°°, M.Ricu°°°, P.Cerretelli°, A.Cabrol*** and C.Cabrol***. Physiology Laboratories Univ. of Geneva°, of Milano°°, of Paris V°°°, of ITBA CNR Milano*; Max Planck Institute f. Exp. Medicine, Göttingen**, and Dept. of Cardiovascular Surgery, Univ. Paris VI***.

Breath-by-breath analysis of respiratory gas exchange and transthoracic impedance cardiography were used to assess the kinetics of adjustment of ventilation ($\dot{V}_E$), O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$) and cardiac output ($\dot{Q}$) in response to upright rectangular cycloergometric loads (50 W, 5 min) in 21 heart transplant recipients (HTR; age 44±8 yrs; 23±29 mo after transplantation, range 1.3-137 mo) and 10 normal healthy subjects (CTL; age 37±10 yrs). The half-times ($t_{½}$, s) of the on-response and off-response are illustrated by the following table (means ± SD; ° p>0.05, • p<0.05, ••• p<0.001).

	CTL (n=10)		HTR (n=21)	
	$t_{½}$-on	$t_{½}$-off	$t_{½}$-on	$t_{½}$-off
$\dot{V}_E$	42±10	30±6	77±16•••	55±16•••
$\dot{V}O_2$	31±10	25±6	53±10•••	46±10•••
$\dot{V}CO_2$	41±11	30±7	79±13•••	57±15•••
$\dot{Q}$	40±17	31±14	52±16°	44±15•

The results demonstrate that in HTR the kinetics of adjustment of $\dot{Q}$ is only moderately impaired in contrast to the significantly slower (about 85%) kinetics of respiratory gas exchange at onset of and recovery from rectangular work loads. It is concluded that, during moderate exercise, the limiting role of $\dot{Q}$ for the individual's physical performance in HTR does not prevail over that in normal subjects.

77.8

EVALUATION OF TWO BREATH-BY-BREATH GAS EXCHANGE SYSTEMS. D.S. Miles, M.H. Cox,* J.P. Bomze,* M. Hlavac,* C.J. Bixby,* and H. Leonard.* The Graduate Hospital Human Performance and Sports Medicine Center, Wayne, PA 19087.

The 2001 metabolic cart and the newer CPX desktop open-circuit gas exchange systems (Medical Graphics Corporation) were compared. Both systems utilize breath-by-breath technology with the same type of O_2 and CO_2 analyzers, pneumotach, and software. The CPX is runs under DOS and the 2001 runs under CTOS (Convergent Technologies). The systems were connected in series during a maximal ramping protocol and steady-state exercise at 75% maximal workload using a Mijnhardt KEM-3 electronic cycle at 60 rpm. Twelve subjects, 7 men and 5 women, completed the two tests on separate days. Maximal oxygen uptake ($\dot{V}O_2$max, ml/min/kg) for the group averaged 7% higher for the CPX (45 vs 42). There were tremendous individual differences between $\dot{V}O_2$max for the two systems with a range of -16 to +17%. Steady-state $\dot{V}O_2$ averaged 6% higher with the CPX for the group with an individual range of differences between the two systems from -17 to +14%. Furthermore, in 8 individuals steady-state $\dot{V}O_2$ disagreed by greater than ± 20% from predicted for both systems. Calibration conformed to company specifications before and after each test. Although the hardware and software are similar for the two systems, it appears that significant differences exist in data reduction.

77.9

ENHANCEMENT OF DIETARY INDUCED THERMOGENESIS BY PRIOR EXERCISE IS NOT CARBOHYDRATE SPECIFIC OR INSULIN DEPENDENT. Thomas W. Balon and Gregory Welk. Univ. of Iowa, Iowa City, IA 52242

Recently, it has been shown that prior exercise potentiates the thermic effect of a glucose load (Young et al. Metabolism 35:1048, 1986) and that insulin may play an important role in this phenomenon (Balon et al. AJP 252:E294, 1986). The purpose of this study was to ascertain whether this phenomenon was specific to different carbohydrate epimers and to determine the importance of insulin. Six healthy males (age 23±2 yr.; wt 75.4±2.7 kg; %fat 7.4±1.4; VO_2max 66.8±1.9 ml/kg/min), exercised for 45 min at 70% VO_2max after an overnight fast. After return to pre-exercise $\dot{V}O_2$ levels, subjects ingested either a 100 g glucose (EG) or 100 g fructose (EF) load. Blood samples and respiratory gas exchange data were collected over the next 3 hrs. On separate days, on which subjects did not exercise, the test procedures were repeated (RG) (RF). $\dot{V}O_2$ increased 26% during RG as compared to 42% during EG. $\dot{V}O_2$ increased 31% during RF vs. 52% over baseline for EF. During neither RF or EF was there an appreciable increase in plasma insulin concentrations. The results indicate that the thermic effect of carbohydrate is not specific for glucose; is not insulin-dependent and may not be specific towards skeletal muscle.(Supported in part by an ADA feasibility grant and a Univ. of Iowa Old Gold Fellowship.)

77.10

FLUID REPLACEMENT DRINKS DURING HEAVY EXERCISE: EFFECTS ON MINIMIZING EXERCISE-INDUCED DISTURBANCES IN HOMEOSTASIS. J. Lawler, S. Powers, S. Dodd, R. Tulley, G. Landry, and K. Wheeler. Ctr for Exer. Sci., U of FL, Gainesville, FL 32611

The purpose of these experiments was to examine the influence of various fluid replacement drinks on exercise-induced disturbances in homeostasis during heavy exercise. Nine trained cyclists performed three separate constant load cycle ergometry exercise tests to fatigue at ~85% of $\dot{V}O_2$ max. During each experiment subjects consumed one of the following beverages prior to and during exercise: 1) non-electrolyte placebo (NEP), 2) glucose polymer drink containing electrolytes (GP; 7% CHO), and 3) electrolyte drink without carbohydrate (EP). Both the GP and EP beverage contained sodium citrate/citric acid (C) as a flavoring agent. Rectal temperature, HR, Δ% plasma volume as well as plasma concentrations of total protein, FFA, glucose, lactate, K^+, Cl^-, Ca^{++}, and Na^+ did not differ during exercise (P>0.05) among treatments. In contrast, blood hydrogen ion concentration [H^+] was significantly lower (P<0.05) at min 30 of exercise in GP and EP compared with NEP. These data provide evidence that drinks containing electrolytes do not minimize disturbances in blood electrolyte concentrations during heavy exercise; however, fluid replacement beverages containing buffers (i.e. C) and/or electrolytes may minimize blood alterations in [H^+] during intense exercise. Supported by a grant from Ross Labs, Columbus, Ohio.

77.11

INSENSITIVITY OF LABORATORY MEASURES TO TRAINING INDUCED IMPROVED PERFORMANCE IN ATHLETES. A. C. Snyder, T. J. Woulfe*, R. Walsh* and C. Foster*. Univ. Wisconsin - Milwaukee, Milwaukee, WI 53201.

For laboratory tests to be useful in the evaluation of athletes, tests must satisfy the twin criteria of correlating with performance and tracking changes in fitness. The purpose of this study was to evaluate cycle ergometry (CE) relative to these criteria. Ten well trained cyclists were studied during incremental CE and during a 20 km time trial (TT) before (PRE) and after (POST) 21 days of intensified training (150% normal). TT performance was moderately well correlated with VO2max (r = -0.61). Comparing PRE to POST TT performance improved (30.4 ± 0.4 to 29.8 ± 0.4 min) (p<0.05). VO2max (5.02 ± 0.10 to 5.03 ± 0.15 l/min) and power output (363 ± 3 to 372 ± 3 watts) failed to change (p>0.05). OBLA (314 ± 4 to 334 ± 3 watts) and the individual anaerobic threshold (188 ± 7 to 235 ± 4 watts) increased (p<0.05). Adjusting for changes in maximal blood lactate (9.4 ± 0.6 to 8.7 ± 0.8 mM) by computing the power output at 30% (271 ± 6 to 289 ± 6 watts) and 50% (324 ± 4 to 336 ± 3 watts) of maximal lactate (p>0.05), suggested no change in the pattern of blood lactate accumulation. None of the changes in CE performance correlate with changes in TT performance. The results suggest that contemporary laboratory measures of the capacity for endurance performance may be largely insensitive to training induced changes in endurance performance in athletes.

Supported by a grant from the USOC.

77.12

ENDURANCE TRAINING EFFECTS ON CARDIOPULMONARY BAROREFLEX SENSITIVITY IN HUMANS. G.W. Mack, C.A. Thompson*, D.F. Doerr*, E.R. Nadel and V.A. Convertino. J.B. Pierce Fndn. Lab., New Haven, CT 06519 and NASA Kennedy Space Center, FL 32899.

The stimulus/response characteristics of cardiopulmonary (CP) baroreflex control of forearm vascular resistance (FVR) were studied in 16 volunteers before and after 10 weeks of endurance training (ET). We assessed the relation between stimulus, i.e. changes in central venous pressure (CVP), and response, i.e. FVR, during selective unloading of CP mechanoreceptors using lower body negative pressure (LBNP) from 0 to -20 Torr. Maximal aerobic power and blood volume (BV) increased (p<0.05) with ET from 37.8±1.4 to 45.3±1.4 ml/(min kg) and 63.6±2.1 to 69.3±2.8 ml/kg, respectively. Reflex forearm vasoconstriction occurred with a reduction in CVP, and the gain of the FVR/CVP response was reduced from -5.68±0.66 to -4.15±0.51 U/Torr (p<0.05) following ET. Resting values for CVP and FVR were similar pre- and post-ET. The reduction in gain of the CP baroreflex was linearly related to the increase in BV (r=0.53, p<0.05), thereby allowing the conclusion that an attenuation in this reflex accompanies BV expansion with ET. However, there was also an increased tolerance (p<0.05) to high levels of LBNP following ET, allowing the conclusion that the attenuated CP reflex does not impair arterial blood pressure regulation during a hypergravity stimulus.

77.13

SUPINE AND UPRIGHT EXERCISE RESPONSES DETERMINED WITH IMPEDANCE CARDIOGRAPHY.
I.A. Barney*, M. Muzi*, J.J. Smith. VA Medical Center and Medical College of Wisconsin, Milwaukee, WI 53226

Ensemble-averaging of impedance cardiograms reduces waveform distortion due to motion artifacts and respiration. We applied this technique to 6 healthy young males at rest and during two levels of bicycle exercise in the supine and upright (seated) positions. At seated rest, heart rate (HR) values (75.7±1.9/min, mean±SEM) were significantly ($p<0.05$) higher and stroke volume indices (SVI)(31.9±2.2 ml) and cardiac indices (CI)(2.35±0.13 l/min) were significantly lower than in the supine position (59.9±1.9/min, 56.5±3.6 ml and 3.26±0.17 l/min, respectively). During exercise in the supine position, the CI increases were due mainly to HR increases but in the seated upright position, the CI increases were due to both HR and SVI increases. These hemodynamic responses were in good agreement with previous studies using other invasive and/or more involved methods to determine cardiac output. The impedance method also provides other useful information. For example, in the seated position, there were decreases in thoracic blood volume (increased Zo) and PEP/LVET, as well as increases in the Heather Index and rapid ejection index. Impedance cardiograms can provide useful hemodynamic information in human subjects during exercise.
(Supported by the Dept. of Veterans Affairs and SORBA Medical Systems, Inc., Milwaukee, WI)

77.14

VALIDATION OF ELECTRICAL IMPEDANCE AND CIRCUMFERENCE MEASURES FOR ESTIMATING BODY FAT. L.G. Myhre, E. Indebritzen,*and D. Tucker.* USAF Sch. of Aerospace Med., Brooks AFB TX 78235

Whole body electrical resistance and selected circumference measures have emerged as attractive alternatives to more technically demanding methods for estimating human body composition. Lukaski et al. (1985) found the electrical impedance method accurately estimated the %body fat values obtained from hydrostatic weight, but several other investigators have not shared in this enthusiasm. Still another and even simpler method using height and 2 or 3 body circumferences (Hodgdon & Beckett, 1984) has demonstrated impressive validity and reliability in this field. Each of these methods were validated in our lab against the standard (underwater weight) in 23 male and 12 female post-absorptive subjects ranging in age from 18 to 49 yrs. Underwater weight was corrected for the volume of air in the lungs determined at the time of weighing and %fat was calculated according to Brozek et al. (1963). Within less than 1 hour measures of electrical impedance and body circumferences were obtained according to published procedures. Correlation coefficients for the relationship between these measures and the standard were 0.43 and 0.95 for the electrical impedance and circumference methods, respectively. These results support the concern expressed by others in the use of the impedance technique; they also lend support to the practical application of the simple circumference technique for estimating %body fat in humans.

TEACHING MATERIALS AND METHODS

TMM.1

CURRICULUM STRATEGIES FOR INTRODUCING STUDENTS TO COMPUTER SIMULATION OF PHYSIOLOGICAL SYSTEMS. M.A.Farrell Epstein Univ. of Connecticut Medical School, Farmington, CT 06032

In view of the growing number of physiologic system simulations developed for microcomputers and the increasing availability of computers for students on most campuses, physiological systems simulation can be considered an aid for student learning as are audio-visual material and advanced texts. One problem that arises is the limited computer experience of some students. To overcome this problem, a curriculum was developed that did not require any prior computer experience and presented as an elective to first year medical students. The curriculum had three goals: 1) to introduce basic concepts used in quantitive modeling of physiologic systems; 2) to describe the framework generally used to organize physiologic systems simulations; 3) to teach approaches for evaluating the validity of a given simulation. The concepts covered included chemical reaction, illustrated by one and two compartment pharmacokinetic models; pressure-flow relationships, resistance and compliance demonstrated by cardiac and circulatory systems simulations; and diffusion with and without chemical reaction illustrated by gas exchange. Programs from different commercial publishers and universities were selected to demonstrate how simulations may be organized. Evaluation of the curriculum suggests that this approach can be used within any course for which relevant simulations are available and may be valuable for faculty curriculum groups.

TMM.2

TWO COMPUTER BASED LECTURES IN CARDIO-VASCULAR PHYSIOLOGY. John P. Meehan. U.S.C. School of Medicine, L.A., CA 90033

Computer based lectures using graphics, animation and animated graphics covering the mechanics of the circulation and the mechanics of cardiac contraction were developed for use by first year medical students and by students in related health care fields. Program format was selected such that a single or a group of five or six students could make effective use of the programs. Experience gained over two years using similar material guided the development of the presentation techniques employed. Each program includes ten study questions. The student may easily access any part of the program desired for review purposes. The programs are particularly useful for those students with limited background preparation.

Both basic and C programming languages were used. Programs run on the IBM PC or equivalent clone and require graphics capability and a color monitor.

TMM.3

ACID BASE SIMULATION IN TEACHING. Alan Dobson and Hugo Borda* N.Y. State Coll. Vet. Med., Cornell Univ., Ithaca NY 14853.

The simulation is intended for use in two contexts - for projection during a formal lecture or class discussion, and for private study either within a physiology course, or during revision during clinical studies. It complements rather than substitutes for laboratory and lectures. The simulation is based on a calculator, with $\ln(Pco_2)$ and BE of the extracellular fluid as the independent variables. A control panel for emulation of titration of extracellular fluid by the addition and subtraction of H^+ or CO_2 is provided. Titration generates an interactive display of the pathways of either the primary disturbances or the secondary responses of a subject. Correction is supplied manually. The appropriate degree of maximal compensation can be automatically invoked. Displays of acid base values can be selected from three numerical and five commonly encountered graphical displays including Henderson-Hasselbach, the buffer interaction reaction and Davenport, Siggaard-Andersen and A.M.A. plots. A description of the operation and assumptions of the simulation, with hints on use, and answers to questions are built in. The program is written in Microsoft C 5.1 and Microsoft Windows, and runs on an IBM PS/2 with 1 Mb RAM and a mouse. A color display and projector supplement the flexibility of the Windows environment. The simulation is available from Wisc-Ware.

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AUTHOR INDEX

The number to the left of the decimal designates the session. The abstract number follows the decimal. A zero indicates that participation was invited and an abstract was not required.

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