THE PHYSIOLOGIST

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# EDITORIAL

## Governance

The birthday present will not be a surprise. When we meet in the seat of the Nation's governance to celebrate the 100th birthday of the American Physiological Society, the Society will unwrap a new governance structure to serve us for the next century.

The Long-Range Planning Committee members submitted recommendations to the APS Council at the Spring Meeting of the Society in St. Louis.*

The basic recommendation is to increase representation of the diverse interests in the Society. To accomplish this, the proposal recommends that we

. . . increase the size of Council,

. . . increase the representation from sections of the Society,

. . . simplify the voting procedures, and

. . . form a nominating committee to accomplish these goals.

The Council will meet in August of 1986 to carefully evaluate the detailed recommendations of the Long-Range Planning Committee. Council's draft of the Plan for Governance of the APS will be mailed to the membership.

Input will be solicited and the proposal will be open for discussion and modification at the Fall Business Meeting of the Society in New Orleans. After the Fall Meeting, Council will meet in retreat format to finalize the proposal along with necessary changes in the bylaws. These documents will be published in *The Physiologist* for review by the membership in

* S. Chien, E. O. Feigl, M. Frank, J. P. Granger, G. A. Hedge, H. E. Morgan, X. J. Musacchia, F. G. Knox, W. C. Randall, M. Siegman, H. V. Sparks, Jr., N. C. Staub, A. E. Taylor, and J. B West.

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# The Peer-Review Process at NSF

**Lewis Greenwald**
*Program Director, Regulatory Biology, National Science Foundation*

There are about a dozen programs at the National Science Foundation (NSF) that fund physiological research. Some of these programs differ in their peer-review procedures in only negligible details, whereas other programs differ from one another in many important respects. The procedures, interests, priorities, and even existence of programs at NSF are dynamic, changing with changing staff and occasionally with internal reorganization. In view of these differences and in view of the dynamic nature of NSF programs, perhaps the best advice that can be given to the physiological community is to call the program officer who seems to be most closely related to the research project in question early in the development of a proposal. That program officer can then advise the principal investigator (PI) of such matters as target dates, changes in program priorities, and special funding opportunities. A list of programs and program officers of potential interest to physiologists appears at the end of this article. The NSF publication *Guide to Programs* is also a useful, albeit brief, source of information on NSF programs. Up to date information can be obtained from the NSF *Bulletin*.

## Assignment of Proposals to Programs

When proposals are received at NSF, they are assigned to the appropriate program by program officers. The PI may direct a proposal to a particular program by filling in the block on the NSF cover page entitled "For Consideration by NSF Organizational Unit." If the program officer who is assigning proposals feels that the PI's choice is reasonable, then the proposal will be sent to the program chosen. Conversely, if the program officer feels the designated program is clearly inappropriate, then the proposal will be directed to that program thought to be most suitable. It is helpful to NSF staff, when assigning proposals, if the PI has given his or her proposal a title that clearly describes the scope of the proposed research. Similarly, a carefully drafted abstract will help to ensure that the proposal is assigned to the most appropriate program. If the proposal concerns an organism, then the abstract should identify that organism. In cases where the scientific name is not well known, the abstract should indicate the sort of organism that will be studied.

Once the proposal reaches a program (perhaps as much as 2–three weeks after receipt), the program officer will make a final determination of the proposal's suitability for that program. In the event that the proposal is not entirely suitable, the program officer will discuss the matter with other program officers to determine which program is indeed the right one for that proposal. The proposal will be formally assigned to the most appropriate program after such discussions. In cases of overlap, it is common for a proposal to be reviewed jointly by two programs. If the two programs are in the same division, then there will be no delay in the review process. If the two programs are in different divisions, a delay of a few months may occur if the two programs have panel meetings at different times of the year. Once a

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preparation for the Spring Meeting to be held in Washington, DC, in 1987.

If these steps can be accomplished, we will adopt the new governance plan at the Centennial Meeting, hopefully an appropriate birthday present but not a complete surprise.

Franklyn G. Knox

NSF
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proposal has found a home, the PI will be so notified.

Proposals that exceed the 15-page (single space) limit for text may be returned to PIs. A PI can then submit a shortened version of the proposal, but the delay involved may mean that the proposal will be held for the next target date which may be 4 or more months away.

The NSF does not support research dealing with human or animal diseases or abnormalities or with drug development. Therefore, proposals dealing with such topics are not accepted for review by the foundation. On receipt of such a proposal, a program officer will typically recommend to the division director that the proposal in question be returned as inappropriate. If the division director agrees, the program officer will inform the PI by phone. A PI can appeal any decision of proposal assignment or suitability to the cognizant program officer or division director. Of course, most problems of proposal assignment and suitability are avoided when PIs discuss their proposals with program officers prior to proposal submission.

## Assignment of External Reviewers

All research programs at NSF send their proposals out for evaluation by external reviewers (so called ad hoc reviewers) chosen by program officers. A suitable reviewer for a proposal is a doctoral level scientist (Ph.D., M.D., or equivalent) who is knowledgeable about at least some aspect of the subject matter of the proposal but who has not worked with (published with or been a student or mentor of) the PI. Of course, scientists from the same university as the PI may not review that PI's proposal. The reviewer may be a mature postdoctoral student. Foreign reviewers are often used. If a PI cares to suggest reviewers to the program officer, the PI should do so in a separate letter. The program officer will usually try to honor in part the PI's suggestions. Care should be taken that the letter suggesting reviewers is not photocopied and included with each proposal copy. Reviewers suggested by a PI should not be from his or her university, nor should they be scientists who have worked with the PI. Occasionally, PIs will mention scientists to whom they would like the proposal not to be sent. Such requests should be made with circumspection and might include a short justification, especially if the potential reviewer is an obvious choice due to emminence in the field. Such requests are generally honored.

Reviewers are selected primarily from the program officer's knowledge of the field, from suggestions by panelists who serve in an advisory capacity to the program, from literature sources such as current journals, from on-line data bases, and, very often, from the bibliography of the proposal itself. Many programs keep files of reviewers who are qualified in particular areas. If a proposal is to be jointly reviewed by two programs, then each program will have the opportunity to suggest reviewers. Typically, proposals are sent to between five and seven reviewers.

## Panel Review

All programs in the Behavioral, Biological, and Social Sciences Directorate (BBS) use panels of outside experts to advise the programs as to the overall quality of proposals. Other parts of NSF may or may not use advisory panels. Typically, a program will have 10–20 panelists on its roster, of whom only 6–10 will attend a given panel meeting. There will be two or three panel meetings per year. Panelists are, in most cases, at the associate or full professor rank. In all cases, they are mature and accomplished scientists who are well known in their fields. A panelist will serve for up to 3 years. Because of the rotation


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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. **If you change your address or telephone number, please notify the central office as soon as possible.**

and turnover of panelists, a resubmitted proposal will be reviewed by a panel with some different panelists than those that reviewed the original submission. New ad hoc reviewers as well as some who reviewed the prior submission are normally asked to review the resubmission.

Well in advance of a panel meeting, the panelists will either be assigned proposals or will be given the opportunity to choose which proposals they would like to read. Of course, panelists will choose (or will be assigned) proposals in their areas of expertise. Generally two (and sometimes three) panelists will read each proposal. Panelists from the same university as the PI may not read or be present during the review of that PI's proposal. Panelists who have worked with (published with or been students or mentors of) a PI may similarly not be present during the review of that PI's proposal. Like the outside reviewers, the panelists who read a proposal will normally prepare written reviews. The panelist reviews, along with the reviews from outside reviewers, will all be sent to the PI once an action has been taken on the proposal. The PI will receive verbatim copies of reviews, without any editing except for occasional brief deletions to ensure anonymity of the reviewer.

Before the panel meeting, outside reviews usually are sent to panelists who are responsible for a given proposal. At the panel meeting, each proposal will be discussed by the two or three cognizant panelists who will review the main issues of the proposal for the panel and program officers. This discussion will focus on such matters as the main question that the work hopes to answer, the approach to be taken, the suitability of the methods, and the qualifications and recent accomplishments of the PI. Particular attention will be paid to the scientific importance and innovativeness of the major theme of the proposed research. The panelists will also discuss the outside reviews. Occasionally, in the opinion of panelists, outside reviewers may appear to be too harsh or too lenient in their evaluations or may, at times, misinterpret an aspect of the proposal. To the extent that this may have occurred, the panel may recommend that the opinions of that outside reviewer be discounted.

During the discussion of the proposal, the panelists will advise the program on the capability of the PI. Such factors as the PI's training and recent productivity are considered. Panelists also note such factors as whether the PI falls into any of the categories that qualify for special funding programs by NSF (e.g., minority, women, or handicapped scientists and scientists from primarily undergraduate institutions). In the case of PIs from undergraduate institutions, appropriate allowances are made for the heavy teaching loads typical of such schools. In no case, will qualification for inclusion in a special funding category compensate for a scientifically weak proposal.

Panelists who may not have been asked to read the proposal may contribute to the discussion to the extent that they are knowledgeable about the topic. After a full discussion, the panel makes a recommendation to the program about its final evaluation of the work and whether it should be funded and at what priority. All of this discussion takes place in the open; no secret ballots are cast. Finally, one of the panelists who has read the proposal will draft a summary of the panel discussion. The other panelists who have read the proposal may edit or add to this panel summary, which, along with the copies of the outside reviews, will be sent to the PI.

## Decision Making

Program officers do not technically make funding decisions at NSF. Rather, program officers recommend to their division directors that a proposal be supported or declined. However, because the program officer is knowledgeable about the science involved, is involved in all phases of the review of the proposal, and is aware of the quality of competing proposals, the recommendations of the program officer are not often challenged by the division director. Indeed, the role of the division director is, in this regard, to assure that the program officer has provided convincing justification for his or her recommendation and that the review process was fair and unbiased. Only after a formal action (approval or declination) has been taken on a proposal will the division forward copies of the reviews and the panel summary to the PI.

The major determinant of which proposals are recommended for funding is scientific merit. Priority is often given to work that will break new ground. Of course, the PI must be judged capable of doing the proposed work, and such a determination involves an evaluation of the PI's training and recent publication record. Each program also has its own series of priorities that may occasionally change in response to changes and new developments in the area of science covered by that program.

In addition to matters of scientific merit, PI capability, and special program priorities, program officers also consider the extent of funding in a given lab. If two proposals (and the two PIs) are more or less equal in terms of scientific quality and PI capability, program officers will often recommend for support a proposal from a PI whose lab is without funding as opposed to a proposal from a PI whose lab is already well supported. Program officers attempt to get new scientists started in their independent research careers. Some preference is given to renewal applications, but only in those cases where previous performance has been good and the newly proposed studies have high scientific merit. Some consideration is given to the balance of proposals within a program. Program officers may seek to provide wide support over the range of science covered by their programs. On the other hand, when a new and exciting area emerges, some concentration of funding in that direction may be called for. Finally, program officers help to implement NSF policies for support of PIs who are underrepresented in US science and for support of PIs from undergraduate institutions.

## Miscellaneous Considerations

At NSF a proposal can either be funded or declined. There is no "approved but not funded" action. If the PI wishes to resubmit a declined proposal, the PI should wait

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### NSF Programs Supporting Physiological Research

Telephone: (202)357-

Cellular Physiology
Dr. Maryanna Henkart, x7377
Regulatory Biology
Dr. Lewis Greenwald, x7975
Metabolic Biology
Dr. William Robertson, x7987
Biophysics
Dr. Arthur Kowalsky, x7777
Psychobiology
Dr. Fred Stollnitz, x7949
Sensory Physiology and Perception
Dr. Carol Welt, x7428
Molecular and Cellular Neurobiology
Dr. Stephen Morris, x7471
Integrative Neural Systems
Dr. Nathaniel Pitts, x7471
Developmental Neuroscience
Dr. Frank Collins, x7428
Population Biology and Physiological Ecology
Dr. James Collins, x9728
Polar Biology and Medicine
Dr. Richard Williams, x7894
Bio-medical Engineering
Dr. William Freedman, x7710
Biological Instrumentation
Dr. John Wooley, x7652

# American Physiological Society 135th Business Meeting

**Time:** 10:00 A.M., Wednesday, April 16, 1986
**Place:** Clarion Hotel, St. Louis, MO

## I. Call to Order

The meeting was called to order by the President, Howard E. Morgan, who welcomed the members to the 135th Business Meeting of the Society. The agenda and ballot for the election of new members were distributed to the members along with a compact for affiliation between APS and the Microcirculatory Society, proposed amendment for society sections and affiliations, and a statement on random source animals.

## II. Report on Membership

The President-Elect, Franklyn G. Knox, reported on the status of membership and deaths since the Fall Meeting.

### A. Summary of Membership Status

The membership of the Society currently stands at 6,303, an increase of 55 members since the October 1985 meeting with increases in all categories. As of March 1, 1986, there are 6,303 members with the distribution of 4,574 Regular, 14 Honorary, 143 Corresponding, 761 Associates, 636 Emeritus, and 175 Student members.

### B. Deaths Reported Since October Meeting

The names of 16 deceased members were read by Dr. Knox. The membership observed a moment of silence in tribute to them (p. 73).

## III. Membership

### A. Appointment of Tellers

Tellers appointed by President Morgan were Ernest Page, Marion Siegman, Patrick Harris, and James McNamee. Members were asked to strike the names from the ballot if they did not wish to vote for a particular candidate.

### B. Election of New Members

It was announced by the Executive Secretary-Treasurer, Dr. Martin Frank, that all candidates were elected, with 163 members casting votes.

## IV. Election of Officers and Affairs of Society Office

### A. Election of Officers

Dr. Martin Frank, Executive Secretary-Treasurer, reported that the election of officers by mail ballot was audited by Drs. Norman Alpert and Jackie Wood in accordance with the bylaws. The new President-Elect is **Harvey V. Sparks, Jr.**, and the two new Councillors are **Shu Chien** for a 4-year term and **Jay A. Nadel** to complete Dr. Sparks' term expiring in 1988.

### B. Affairs of Society Office

The Society has undergone a transition since Dr. Frank's arrival in July 1985. The Society is also going through a period of transition in terms of physical facilities at the APS headquarters with the construction of a new wing of the Lee Building in Bethesda. Dr. Frank extended an invitation to the membership to visit the APS offices on the Beaumont campus in Bethesda during the APS Centennial Celebration Meeting to be held in Washington, DC, from March 29 to April 3, 1987. The Society has entered the computer age and has benefited from the purchase of an Intel Super Microcomputer for word processing and data management.

In addition to the physical changes, there have been a few staff changes. Mr. Walter Sonnenberg, who was the Business Manager for 19 years, retired in March, and Mr. James Liakos has assumed this position. Dr. Joseph Saunders has resigned to become the Executive Officer of the American Association of Immunologists and his assistant has taken a position with the American Society for Pharmacology and Experimental Therapeutics. While Dr. Saunders' departure has caused some disruption, Dr. Frank was pleased to report that an additional staff person has been added to facilitate the Society's ability to interact with the membership and respond to their needs. Dr. Frank took the opportunity to introduce the APS staff members in attendance and expressed appreciation for their efforts on behalf of the Society.

## V. Amendment to the Bylaws

The proposed amendment, Article X. Section 2. Society affiliations, to the Bylaws to authorize affiliation of societies having mutual interests to the Society upon approval of the membership, was published in the December 1985 issue of *The Physiologist*. The change in the bylaws is necessary to allow the completion of an agreement with the Microcirculatory Society.

*A motion was seconded and passed unanimously that Article X, Section 2. Society Affiliations of the bylaws be amended by adding the sentence "The Council shall authorize affiliation of societies having mutual interests to the Society upon approval of the membership."*

## VI. Compact for Affiliation with the Microcirculatory Society

During the past several years, the APS Council has been in the process of negotiating possible affiliation with a number of societies in the field of physiological sciences that possess mutual interest and goals of the American Physiological Society. It also provides a mechanism to stimulate new growth and interests in the Society. As a result of these discussions, Council has proposed an affiliation between the Microcirculatory Society and the American Physiological Society. The concept of affiliation has arisen because both groups have a mutual interest in certain areas of scientific investigation and reporting. The two societies draw some of their membership from the same segment of the scientific community. The affiliation of the Microcirculatory Society with APS should enable them to accomplish their purposes and to improve communications between them. As part of the compact for affiliation, APS will provide the Microcirculatory Society with a number of services for which the Society will be reimbursed. In addition, the Affiliate members will have access to a number of Society privileges as described in the compact, which has been approved by Council and the Microcirculatory Society and published in the February 1986 issue of *The Physiologist*.

*A motion was seconded and passed unanimously approving the compact between the American Physiological Society and the Microcirculatory Society to become the first Affiliate Society.*

## VII. Awards

A. **Ray G. Daggs Award** (see p. 55).

B. **Caroline tum Suden Professional Opportunity Awards** [*The Physiologist* 29(3): 41, 1986].

C. **John J. Perkins, Jr. Memorial Fellowship Award** [*The Physiologist* 29(3): 41, 1986].

D. **Senior Physiologists Fund Award** (see p. 68).

## VIII. State of the Society

### A. Publication Activities

Dr. Morgan reported that the membership is growing and most of our activities are expanding. In regard to APS publications activities, two new journals have appeared this year. *News in Physiological Sciences* is a joint publication with the International Union of Physiological Sciences, and Dr. Knut Schmidt-Nielsen is Editor of the publication. There have been many favorable comments on the appearance of the first issue in February. As part of this same reorganization, *The Physiologist* has become a newsletter for Society news and two issues have appeared in this new format with Dr. Martin Frank as Editor. It is a much more interesting and readable publication that is focused on the interests of the Society. It will be a good way for the leadership of the Society and staff to communicate with the members.

The overall publications of the Society continue to grow. The number of manuscripts received in 1985 was 4,059, of which 2,100 were published totaling 19,195 published pages. A disturbing feature in publications is the continued drop in the number of subscribers, down 4% from last year. The total subscribers in 1985 were 15,502. Income of the journals increased 16% in 1985, while expenses increased 8%. As a result, the journals had income over expenses of approximately $640,000. Overall, the journals are in a strong position with reserves totaling approximately $4.3 million, which is roughly one year's operating budget for the journals program.

### B. Program Activity

The other major activity of the Society is in program activity. The ability to present very effective and well-thought-out programs is the other main part of the Society's business. The Council and Program Committee has undertaken efforts to strengthen scientific programs of the Society. The first thing that has been done is to adopt a new thematic approach to the Fall Meeting that is based on interests of individual sections or group of sections.

At the meeting in New Orleans, October 5–9, 1986, the themes will be **Neurohumoral Regulation of Water and Electrolyte Balance** and **Physiological Limitations to Performance, A Comparative Approach**. The thematic approach seeks to attract members, nonmembers and perhaps in the future other societies with common interests. The solicitation of funds from the pharmaceutical industry has been centralized in the Society office to reduce the burden on symposia organizers and to coordinate the approach to any particular company.

A program endowment fund has been established with commitments from The Upjohn Company and the Schering Corporation of $25,000 each. A committee chaired by Dr. Ted Cooper is approaching other pharmaceutical companies with the goal of raising $250,000 toward a program endowment. With these monies and other gifts and Society funds, it is hoped to establish an endowment of $1 million and a yearly income of approximately $100,000 to enhance our program activities. This should provide the resource and also much more effective programs than have been available to the Program Committee in the past.

### C. Society Organization

The other area in which there is a lot of activity at the moment is in the Long-Range Planning Committee and Section Advisory Committee, which have been working to strengthen the sections and to modify sectional governance. These actions include the implementation of current section organizational arrangements and further definition of what performance and expectations we should have for sections. Some sections are quite well organized, have business meetings, and consult with members, while other sections are more informal.

The purpose of trying to make changes in sectional organization is to make it possible to use sections in governance of the Society with assurance that these sections represent a group of at least 100 Regular members who indicate that a given section is their primary interest. Distinctions will be made between an interest group and a section. Interest groups may have less than 100 members with a primary interest in that particular topic and may function even within a section or cross a number of sections. Plans to involve the strengthened sections in governance have been formulated by the Long-Range Planning Committee, which reported to Council at this meeting. The Council plans to meet during the summer to formulate a new governance plan. The goal is to involve more sections in the membership of Council and among the officers. The Council expects to have a proposal ready for submission to the membership by the Fall Meeting.

### D. Centennial—March 29–April 3, 1987—Washington, DC

Finally, the APS Centennial will be celebrated at the Spring FASEB Meeting, March 29–April 3, 1987, in Washington, DC. Dr. Alfred Fishman is Chairman of the Centennial Celebration Committee. Drs. Orr E. Reynolds and Martin Frank and Mr. William Samuels have been coordinating the activities in the Society office for preparation of this celebration. The Centennial Meeting will include an opening ceremony and reception to be held at the Washington Hilton. The general scientific theme will be "A Century of Progress in Physiology," organized by Dr. Michael Jackson. Twenty-five international guests have been invited to the Centennial Meeting and will participate in symposia, present plenary lectures, and give opening talks at the contributed papers sessions. Two evenings at the Kennedy Center are being arranged. A closing reception for APS members at the National Academy of Sciences is being planned, which will involve a lecture and reception. A medallion has been struck in celebration of the Centennial and is available for purchase. It is a very attractive medallion designed by a Society staff member, Ms. Susie Mann.

The 1987 Fall Meeting will continue celebration of the Centennial and will be held in conjunction with the Latin American Association for Physiological Sciences in San Diego.

Dr. Morgan said we should be pleased with the progress of our Society and our science and we look forward to the celebration of our Centennial and a great time next year (see p. 66).

## IX. New Business

### A. Random Source Animals

A statement on random source animals, included with the agenda, was presented to Council by Dr. Aubrey Taylor at the 1985 Fall Meeting with the request that it be included on the 1986 Spring Meeting agenda for submission to the membership. The following statement, approved by Council, is for consideration of the membership:

> Random source dogs and cats (unclaimed pound animals) have proven to be useful research animals. The use of these animals in controlled environments assures proper treatment and health care and provides a vital source of new clinical and basic information. The American Physiological Society strongly endorses the humane use of random source animals for biomedical research.

In support of this proposal, Dr. Taylor does not think many of you have any illusions about what is happening to the use of pound animals across the United States. When we confront the people who do not want pound animals used within our cities, there is no firm statement from the Society that can be used. There are many statements about how good research is and how mankind

has been helped, but it does not satisfy politicians. Therefore, it is extremely important that the American Physiological Society goes on record that the use of pound animals is an important source of research material for the physiological work.

APS member David Gross of Texas A & M University proposed amending the statement to make it stronger and more positive by replacing the first sentence with "The use of random source dogs and cats (unclaimed pound animals) has provided scientific advances that would have been impossible without their contribution," which Dr. Taylor found acceptable.

Dr. Arthur Guyton further proposed making the statement stronger. Having just gone through this fight in Jackson, MS, Dr. Guyton said that, within the last three weeks, Jackson was the first city in the United States where a pound law has been reversed. By virtue of reversing it, they ran into all the statements by the US Humane Society and knew what they were up against. Strangely enough, the worse statements came from NIH. There were several people, some of whom had retired, who made the statement that NIH does not use nor will it use pound animals. One retiree very high up in NIH made a public statement nationally to the effect that pound animals are not useful as research material because they must be bred to know their genetic history. In Jackson, it had to be pointed out that diversity is needed. Therefore, a very strong statement is needed.

In addition to amending the first sentence as recommended by Dr. Gross, Dr. Guyton proposed changing the statement as follows:

> Random source dogs and cats (unclaimed pound animals) have proved to be among the most useful of all research and teaching animals. The American Physiological Society strongly believes that the denial of pound animals for research purposes is an extremely serious loss to both basic and clinical biomedical research and teaching.

Expressing no objection to the change, Dr. Taylor realized it would be an extremely delicate statement to prepare, which is the reason he made it as simplistic as possible.

*A motion to adopt the statement proposed by Dr. Guyton was seconded and passed with one dissenting vote.*

In a subsequent session, Council, in consultation with Dr. Guyton, amended the resolution as follows:

> Unclaimed pound animals (random source dogs and cats) have proved to be the most useful animals for the purpose of research and teaching. Medical advances benefiting both humans and animals were possible because of the availability of unclaimed pound animals for use in research. The American Physiological Society strongly believes that denial of the availability of random source animals would be a catastrophic setback and the Society strongly endorses the continued use of unclaimed pound animals for basic and clinical research and teaching.

B. IUPS Congress

Dr. James Bassingthwaighte, Chairman of the US National Committee for IUPS, reported that the IUPS Congress to be held in Vancouver, BC, July 12–19, 1986, is doing well. The International Program Committee and the Canadian Organizing Committee have done a magnificent job of organizing a program of 100 symposia. Many of our members have made excellent suggestions for the program. Rather few of them emerged unchanged in the process of bringing everything together. The result is a program that brings about an international flavor. Registration has reached 3,100, of which 700 are speakers. The Canadian Organizing Committee is having difficulty holding on to the hotels because of the Expo. Therefore, members who have not registered are urged to do so and to remind their friends.

With no other business, the meeting was adjourned at 11:00 A.M., April 16, 1986.

Franklyn G. Knox, President-Elect

## ORR REYNOLDS AWARD

**The Orr Reynolds Award will be 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 receive 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 appointed 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 professional historian.**

**Manuscripts should be typed and double-spaced with wide margins on 8½ x 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 1987 award, manuscripts should be sent to Orr Reynolds Award, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814, by December 1, 1986. The recipient of the award will be announced at the 1987 spring meeting.**

# Ray G. Daggs Award, 1986

The Ray G. Daggs Award is given for distinguished service to physiology and the American Physiological Society. The 1986 recipient of the Award is Dr. David Bruce Dill, who is 95 and is the patriarch of American physiology. His research has contributed to our understanding of how the body copes with stressful conditions. His book *Life, Heat and Altitude*, first published in 1938, remains a classic. This theme was continued in another book with A. Bock in 1981, *Physiology of Muscular Exercise*. His most recent book. *The Hot Life of Man and Beast*, appeared last year. Dr. Dill's type of research emphasizes the whole body. Holistic medicine as supported by Dr. Dill reverses the reductionist trend in much of current-day physiology.

Several periods stand out in Bruce Dill's career. The first was then the Harvard Fatigue Laboratory centered about him as a leader and successor of L. J. Henderson. During this period he led numerous expeditions, most notably to the high Andes, and built a laboratory of environmental physiology.

Then came his military years when he served in the Quartermaster Corps, working in many extreme environments on earth. Construction of Boulder Dam might have failed without his practical advice. Later, he served at the Army Chemical Center as an administrator and physiologist. An example of his achievements was the perfection of the mouth-to-mouth method of resuscitation. For his military service, Dr. Dill received the Legion of Merit.

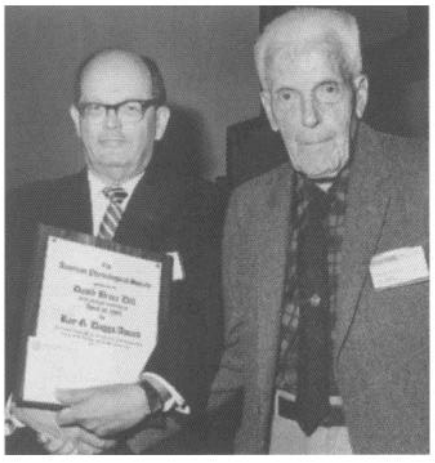
A third period was at Indiana University, where he collaborated with Sid Robinson. Finally came his long years of research in the Nevada desert, where he still subjects himself to exercise and stresses of heat and dehydration together with the further stresses of age.

Dr. Dill's service to the American Physiological Society began at the first meeting after World War II in 1946, when he was elected Treasurer. Elected President-Elect in 1950, he began his term as President in July 1950 after the death of President Henry Cuthbert Bazett. On Council, he took part in the major reorganization of APS Publications, resulting in the appointment of Milton O. Lee as Managing Editor and the move of the society offices to Washington, DC. He was on the first Board of the *Journal of Applied Physiology*, which began publication in 1948. He initiated the tradition of the Presidential tour and helped to organize the first such tour for his successor, E. M. Landis. As Chairman of the Executive Committee of FASEB, he helped formulate the rules under which the Federation now operates. He edited and contributed to *Adaptation to the Environment* of the *Handbook of Physiology* in 1964. Perhaps he is most remembered for his role in creating and nurturing the Senior Physiologists Committee, one of the oldest standing committees of the Society. He founded the committee in 1952 and served as its Chairman until 1980.

It is fitting for the American Physiological Society to honor a distinguished physiologist who has served our science and our society through several generations and in so many ways.

There was a standing ovation as Dr. Morgan presented a check and plaque, which was inscribed, "The American Physiological Society presents to David Bruce Dill at its annual meeting on April 16, 1986, the Ray G. Daggs Award in recognition of distinguished service to the Society and to the science of physiology."

Responding Dr. Dill said, "Thank you very much. I would like to express my appreciation to those responsible for this award and the members of the Ray G. Daggs Committee. Dr. Daggs was my good friend dating back to the days when he was Scientific Director of the Army Medical Research Laboratory at Ft. Knox and continued to be my friend throughout his life. He was a great man and a great member of the American Physiological Society. I thank Dr. Morgan and the members of the Council for approving the award. This is a great society of which I am very proud to be a member. Thank you and God bless you all."

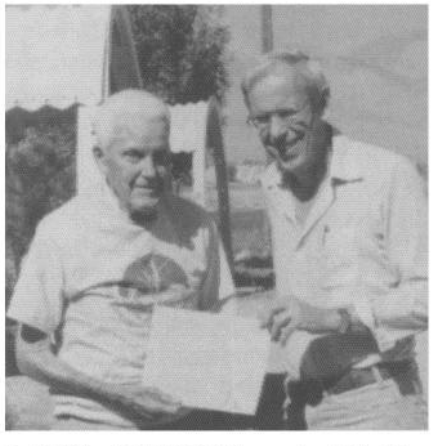


H. E. Morgan and D. B. Dill

## David Bruce Dill (1891–1986)

The Society has lost a stalwart supporter and its 23rd President with the death of Bruce Dill on June 18, 1986. Dr. Dill, born in Kansas but raised and educated in California, spent most of his academic career at Harvard University with the Fatigue Laboratory. Following this he served with the U.S. Army in the Air, Quartermaster and Chemical Corps, notably as Scientific Director of the Army Chemical Center. His work in Environmental Physiology also spanned studies in high altitude, tropic and direct environments to which he continued to contribute until his death.

His congenial disposition and ever-helpful demeanor will be sorely missed by his many friends and colleagues in APS.



D. B. Dill and C. Hall, 1985 Symposium White Mountain Research Station.

## Recipients of Ray G. Daggs Award

| | |
|---|---|
| 1974 | J. 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 |

**APS Presidents**

*Second row, left to right:* F. J. Haddy, A. C. Guyton, H. E. Morgan, A. P. Fishman, J. B. West, and W. C. Randall.
*Front row, left to right:* F. G. Knox, E. H. Wood, A. C. Barger, B. Schmidt-Nielsen,; C. L. Prosser, and H. Rahn.

# Committee Reports

## Porter Development

Fellowship funds are available for able minority students both at the pre- and post-doctoral level. The current predoctoral fellows being supported by the Porter Development Committee are Karen Anderson, who is a candidate for the Ph.D. degree in the Department of Physiology and Biophysics at Colorado State University; Joyce A. Hunter, who is a candidate for the Ph.D. degree in the Department of Physiology and Biophysics at Howard University; Jean A. King, who is a candidate for the Ph.D. degree in the Department of Biology at New York University; and Darlene K. Racker, who is a candidate for the Ph.D. degree in the Department of Physiology and Biophysics at Chicago Medical School.

The postdoctoral fellows are Dr. Carlos A Jiminez-Rivera, who is a fellow in the laboratory of Dr. Rene Drucker-Colin in the Department of Physiology at the Universidad Nacional Autonoma de Mexico; and Dr. Claude Saint-Come, who is a fellow in the laboratory of Dr. John C. S. Fray in the Department of Physiology at University of Massachusetts Medical Center. (Dr. Saint-Come is the first postdoctoral fellow to work in the laboratory of a former Porter Development Fellow, i.e., the second generation, a welcome milestone.)

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, Drs. Pamela Gunter-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 Minority Student Summer Research Internship Program in the Department of Physiology at Michigan State University and 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. Mr. Errol Williams of Princeton University was again a summer fellow in the laboratory of Dr. George M. Langford at Woods Hole. Drs. W. F. Ganong, a former President of APS, and Dr. A. C. Barger visited the Indian Program at University of Minnesota Medical School at Duluth to help in the planning of a joint program with the Porter Development Committee.

The committee has been asked how many minority members there are in the APS. The latest figures are Americn Indian or Alaskan, 7; Blacks, 33; and Hispanic heritage, 82. Since these numbers are small and representative of the situation of minority scientists in other fields as well, the Ford Foundation has recently inaugurated a predoctoral and postdoctoral program that is to be administered by the National Research Council. Eligible candidates in physiology may obtain application materials from the Fellowship Office, National Research Council, 2101 Constitution Ave., Washington, DC 20418.

We again express our appreciation to the Harvard Apparatus Foundation for its continuing support of the Porter Development Program. We also acknowledge gifts from the Procter and Gamble Company, the American Cyanamid Company, and individual members of APS.

**A. Clifford Barger,**
**Edward W. Hawthorne,**
**Co-Chairmen**

## Public Affairs

An effort initiated in late 1982 by the Public Affairs Committee (PAC) came to fruition in December when the Congress approved the 1985 Farm Bill.

In a move to counter the legislative restrictions sought by animal rights groups, the Society suggested in 1982 a proposal to amend some provisions in the Animal Welfare Act as a congressional alternative to creating new legislative authorities governing the care and use of laboratory animals. The Society's proposed amendments to the Animal Welfare Act were included in the Farm Bill.

The amendments do little more than bring the Animal Welfare Act into alignment with the revised Public Health Service policies on the care and use of laboratory animals, but their enactment does represent a public relations victory for the scientific community. In recent years, the scientific community developed a negative public image because of its opposition to all animal-reform proposals. Moreover, the moderate animal welfare groups joined in support of the APS proposals despite continued opposition by the hard-line animal rights organizations.

A second APS proposal—making break-in, theft, or vandalism at federally funded research institutions a federal offense—was introduced in the House of Representatives, but has yet to garner support for consideration.

In other activities the PAC supported a congressional effort to block an administration proposal to reduce from 6,500 to 5,000 the number of new and competing NIH grants in FY85. A compromise 6,100 grants was agreed upon. The PAC also supported renewal of authorizations for NIH, which the Congress approved in an override of a presidential veto.

The PAC was unsuccessful in its efforts to obtain a Congressional Resolution designating November 21 as "William Beaumont Day." The Senate did approve the resolution honoring the 200th birthday of this pioneer in American physiology, but the resolution failed to gain the necessary support in the House of Representatives.

During the year, the PAC conducted two workshops for committee members. In April a workshop, "How to Form a State Coalition," was held in Anaheim and in October a case study as to how the University of Western Ontario turned a smear campaign by animal rights groups into public support for the institution's animal research program.

The PAC's staff support person, William M. Samuels, CAE, consulted with several member institutions about local animal rights activities and was invited to present overviews of the animal issues at the University of Louisville, Cambridge University in England, and the Association of Chairmen of Departments of Physiology meeting in Houston.

John T. Shepherd,
Chairman

## Publications

The vitality of the publications of APS was again evident in 1985. The journals and books continue to meet the needs of physiologists worldwide and to promote the recognition and prestige of the Society.

The number of new manuscripts received for the journals increased by 381 (+10%) compared with 325 (+9%) in 1984. The largest increases were in *AJP: Regulatory, Integrative and Comparative Physiology*, +112 or +32%; *AJP: Gastrointestinal and Liver Physiology*, + 8.6 or +25%; and the *Journal of Applied Physiology*, +89 or +9%. The number of manuscripts submitted as Rapid Communications increased by 83 or 69%. Thirty-eight manuscripts were received for the reinstated Modeling Methodology Forum. The acceptance rates for all manuscripts were about the same as last year, 59%.

The number of articles published in 1985 increased by 2% and the number of text pages by 3%. Increases in the number of pages published, compared with 1984, occurred in the *Journal of Neurophysiology*, +560 or +20%; the *Journal of Applied Physiology*, +508 or +13%; and *AJP: Heart and Circulatory Physiology*, +281 or +14%. Since the journals were reorganized in 1976 the number of articles published has swelled from 1,031 to 2,100 and the number of pages from 8,121 to 19,295.

The number of paid subscriptions continued to drop down from 16,084 in 1984 to 15,502 in 1985, a decline of 4%. Subscription prices were increased by between 11% and 40% for 1985. Printing costs increased by 7% to pay for 3% more pages printed. Total income increased by 16%. Page-charge, reprint, interest, dividend, and royalty income was higher; back and single issue income was about the same; and advertising and alteration income was lower. Total expenses increased by 8%. As fewer pages were published than anticipated the amount of income over expenses was larger than anticipated. As a 20% increase in the amount published is projected for 1986, the journals should be operating closer to break even this year.

Plans were developed and implemented to publish *The Physiologist* as a bimonthly 16-page newsletter beginning February 1986. It will contain mostly Society business and articles of interest to members. The abstracts of the Fall Meeting will still be published in the August issue. The Society continues to show its interest in bridging basic science and clinical medicine through the publication of "Physiology in Medicine" in *Hospital Practice*. An agreement was signed by the Presidents of IUPS and APS for the publication of *News in Physiological Sciences* (*NIPS*). *NIPS* is to be a 48-page bimonthly journal jointly owned and copyrighted by IUPS and APS. APS is the managing publisher operating through a joint managing board composed of two members from IUPS and two from APS. NIPS will be mailed to members with *The Physiologist*.

Five books were published in 1985: *1) Circulation and Nonrespiratory Functions* (*Handbook of Physiology, The Respiratory System*); *2) Interaction of Platelets With the Vessel Wall* (Clinical Physiology Series); *3) Effects of Anesthesia* (Clinical Physiology Series); *4) Voltage and Patch Clamping With Microelectrodes*; and *5) Animal Stress*.

The program continues to be operated on the premise that sufficient income can be recovered from the sale of books in inventory to break even. However, because book sales are not at the high level they once were and the use of books is changing, the Publications Committee laid the groundwork for an extensive review of the book program in 1986.

For 1986 we look forward to an increased amount of quality physiology being published in the journals, including a monthly *AJP: Cell Physiology*. We also are excited by the inauguration of *NIPS* and *The Physiologist* in its new format. No less exciting is the advent of additional *HANDBOOKS* and the 10th book in the Clinical Physiology Series. This year should also see the full text of the *Journal of Applied Physiology* become available on-line.

This extensive publications project would not be possible without the impressive commitment of editors, editorial board members, and reviewers. On behalf of the members of the Publications Committee (W. F. Ganong, L. R. Johnson, F. G. Knox, and J. McE. Marshall), I wish to thank them for their efforts.

Paul C. Johnson,
Chairman

## Women in Physiology

The committee convened January 1986 by phone conference to discuss the ranking and selection of abstracts for the Caroline tum Suden Professional Opportunity Award. There were 28 abstracts submitted from 12 graduate (6 female and 6 male) and 16 postdoctoral fellows (2 females and 14 males). The total number included 8 females and 20 males. One was currently pursuing a joint M.D./Ph.D. curriculum. Only one was a member of the American Physiological Society and one was a member of the American Society of Pharmacology and Experimental Therapeutics.

The approximate distribution by disciplinary field representation of all the abstracts and of the awardees included:

| All Abstracts | | Awardees |
|---|---|---|
| Cardiovascular | 10 | 3 |
| Renal | 6 | 1 |
| Endocrinology | 1 | |
| Gastrointestinal | 2 | |
| Respiratory | 2 | 1 |
| Cellular | 4 | 1 |
| Neurophysiology | 3 | |

The following were chosen for the Caroline tum Suden Professional Opportunity Award on the basis of scientific merit: Mark S. Alsberge, Hahneman University, graduate student; Cathy A. Bruner, University of Michigan, postdoctoral trainee; Katherine J. Lucchesi, Dartmouth University, graduate student; Rick G. Schnellman, Duke University, postdoctoral trainee; Kathleen A. Thompson, University of Pennsylvania, graduate student; Margaret R. Warner, Northwestern University, graduate student.

The committee in conjunction with the Women in Pharmacology Committee sponsored a talk of broad career interest to both male and female scientists. Drs. Marlowe Erickson and Mary Erickson spoke at the FASEB meetings on April 16, 1986. Their topic was "Issues Facing Dual Career Cou-

**APS Council**

*Second row, left to right:* P. C. Johnson, C. V. Gisolfi, A. E. Taylor, H. V. Sparks, Jr., N. C. Staub, S. Chien, and M. Siegman. *Front row, left to right:* M. Frank, H. E. Morgan, F. G. Knox, and J. B. West.

ples: The Problems, Options, and Resolutions."

The committee continues to encourage the APS to support a speaker at the FASEB meetings. In this regard, the committee is collecting names of potential speakers for the 1987 FASEB meetings.

The Women in Physiology Committee convened again in St. Louis at the FASEB meetings on April 15, 1986 (Helen J. Cooke and Hugh van Liew in attendance), and again on April 17, 1986, with Dr. Martin Frank and Dr. Toby Appel.

The committee continues to be concerned with the lack of representation of women physiologists as candidates for employment at various institutions around the country and the lack of representation of women on scientific study sections and on seminar speakers' lists. This lack of representation of women in leadership positions is apparent in the American Physiological Society as well. This includes lack of representation of women scientists on APS committees, editorial boards of the *Americal Journal of Physiology*, as chairpersons of symposia and scientific sessions, and on the Council. To this end, the committee will be identifying potential women who might serve on various Society committees as well as serve as chairs or speakers or on study sections. The committee will be sending out a questionnaire to identify interests, academic positions, and research support of female physiologists in the future.

One issue that was raised and acted on by the committee includes continued APS support for a Women's Scientists' Lounge in the Convention Center. Another issue that affects both female and male scientists is the high cost of hotel accommodations, particularly for the scientist who has no one to share the room. In this regard, the committee, on recommendation from the Women Scientists' Caucus, gave support to the roommate service concept. If a person is interested in sharing the cost of a room with someone else, they would check a box on the registration forms. A list of available persons would be made available for them to contact through the APS office. The committee hopes that this will be implemented for the 1987 FASEB meetings in Washington, DC.

Day-care arrangements continue to be a concern of many physiologists who attend the Society meetings. The Women in Physiology Committee is working with the Women's Committees in Pharmacology and Immunology and the Women Scientists' Caucus to identify possible ways of implementing such arrangements.

Helen J. Cooke, Chairperson

# Section Reports

## Comparative Physiology

The Comparative Physiology Section held its annual business meeting at the APS Fall Meeting in Niagra Falls as well as an informal meeting at the FASEB meetings in St. Louis. The executive of the section for 1985/86 consists of Donald C. Jackson, Chairman; R. Blake Reeves, Past Chairman; Roger M. Fedde, Councillor; Larry I. Crawshaw, Program Advisory Committee Representative; and William K. Milsom, Secretary.

Extensive discussions at both meetings centered around the format of the Fall Meeting and the commitment of the section to this meeting. In 1979 at its second business meeting, the section identified the Fall Meeting as the official meeting of the section. It was further proposed that this meeting be held jointly with the Division of Comparative Physiology and Biochemistry of the American Society of Zoologists every other year. The next joint meeting is scheduled to be held in San Diego in the fall of 1987. The section is still committed to these proposals and concerns surrounding the change of the Fall Meeting to a theme-oriented meeting have been largely alleviated. Given this change in format, however, and the commitment of the section to the Fall Meeting, section members should begin submitting suggestions of themes and a program for the 1987 meeting to Larry Crawshaw (Dept. of Biology, Portland State University, Portland, OR 97207). These proposals will be considered at the meeting of the Program Advisory Committee to be held at the Fall Meeting in New Orleans this October.

Discussions concerning the establishment of a young investigator award for the best abstract and presentation in comparative physiology at the annual Fall Meeting have finally reached fruition. The Scholander Award will be presented for the first time this year. An announcement containing the details of the award appears elsewhere in this issue of the *Physiologist* and will also be sent to all members of the section. The award will be presented at a fund-raising dinner to support the award during the Fall Meeting in New Orleans. Details will be sent to all members at a later date. Members of APS and friends of Professor P. F. Scholander are encouraged to contribute to the Scholander Award Fund. Contributions are tax deductible, and checks should be made payable to the American Physiological Society with the notation "Scholander Award Fund."

W. K. Milsom, Secretary

## Gastrointestinal

The past year was distinguished by an increase in established activities and by the institution of new programs. The year began with the installation of two new Councilors to the Steering Committee, Dr. Helen Cooke and Dr. John Williams; and a new Secretary-Treasurer, Dr. Herbert Ormsbee III. The summer saw the successful completion of the first FASEB Summer Conference that was organized by the Gastrointestinal Section, mainly through the efforts of Dr. Lenard Lichtenberger, who serves as the section representative to the Program Advisory Committee of APS. This 5-day conference on gastrointestinal development attracted 125 scientists from around the world who discussed epithelial, neural, muscle, and endocrine tissue. The fall and winter were spent on efforts to increase the membership, on working with APS to strengthen the role of the sections in APS governance, in instituting an awards program designed to recognize and encourage students and postdoctoral fellows who are concentrating their efforts in gastrointestinal research, and in planning for the next year. These efforts were rewarded by an increase in members, by an increased voice in APS activities through participation in the Section Advisory Committee, and by the application of 19 young investigators to the Awards Program. The year's activities came to a successful completion this spring during the FASEB meeting. The Gastrointestinal Section combined with the Epithelial Transport Group to sponsor a symposium entitled "Ionic Control of Gene Expression." Additionally, we held our annual meeting. At this 36th meeting of the section, Dr. Jackie D. Wood spoke on "Enteric Neurophysiology" and was awarded the Hoffman-LaRoche Prize in Gastrointestinal Physiology in recognition of his meritorious work in gastrointestinal research. Also, the first two recipients of the Young Investigator Awards were recognized. Mr. Sultan Ahmad was commended for his predoctoral work, "Neurotensin Receptors in Canine Intestinal Smooth Muscle," in conjunction with Drs. J. P. Vincent and E. E. Daniel, McMaster University. Dr. Hannah V. Carey was commended for her postdoctoral work, "$M_2$ Receptors Mediate the Cholinergically Evoked Cl-Secretory Response in Guinea Pig Ileal Mucosa," in conjunction with Dr. H. J. Cook, Ohio State University. Prior to and during the Spring Meeting, plans were made for the future. Based on recommendations

from the membership, two symposia are being organized for presentation during the 1987 FASEB meeting: one on satiety and one on macromolecular uptake in epithelium. Also, a FASEB-sponsored summer conference on adaptation is being organized for 1987 under the direction of Dr. Leonard Johnson. Finally, tentative plans were made for a dinner during next year's annual meeting that will be held in Washington, DC.

Norman Weisbrodt, Chairman

## Teaching of Physiology

The newly formed section was first convened this past April in St. Louis. Among the responsibilities to be undertaken by the section are overseeing the Learning Resource Center, organizing programs to update faculty in particular areas (to be coordinated with the themes of each meeting), and reviewing current approaches to teaching that material.

During the meeting a number of key issues were discussed. The following were the major issues and concerns which members would like the section to address. *1)* Review physiology curricula (in professional, graduate, and undergraduate schools) to establish guidelines. This should be done to assess its present status and its future direction. This was viewed as being of prime importance to ensure that physiology education keeps pace with an ever evolving science. *2)* Establish a forum for those individuals primarily involved with physiology teaching in which they may present papers, publish, and thus distinguish themselves so as to gain national peer recognition. *3)* Determine the role and future of the student laboratory in physiology courses. *4)* Generate a comprehensive listing of baccalaureate, masters, and doctoral programs that offer degrees in physiology.

Specific activities planned by the section for the immediate future include cosponsoring sessions dealing with integrative study in physiology and medicine at the Fall Meeting in New Orleans and sponsoring a half-day symposium on teaching of problem solving in physiology at the Spring 1987 Meeting.

The Teaching of Physiology Section will meet in New Orleans in the fall. All who are interested are welcome to attend. The Steering Committee of the section consists of the following officers: Chairman, Ronald D. Carlin, Fairleigh Dickinson University; Secretary/Treasurer, Edith Rosenberg, Howard University; Councilor, David Bruce, Wheaton College; Program Advisory Committee Representative, Joel Michael, Rush Medical College; and Section Advisory Committee Representative, Harold Modell, University of Washington.

Ronald D. Carlin, Chairman

## Water and Electrolyte Homeostasis

The business meeting for the Section on Water and Electrolyte Homeostasis was held at the FASEB meeting in St. Louis on April 15, 1986. The following items of business were discussed.

### Election of New Officers

Elections for a new Councillor and Program Committee Representative must be carried out prior to July 1. The nominees for the position of Councillor for 3 years were Dr. Gabriel Navar (University of Alabama, Birmingham) and Dr. Ian Reid (University of California, San Francisco). The nominees for Program Committee Representative were Dr. Alan Kim Johnson (University of Iowa, Iowa City) and Dr. Edward Blaine (Washington University School of Medicine, St. Louis). Ballots for this election are included with the newsletter, and the membership of this section is urged to return their ballots as soon as possible to APS. Present officers are Allen W. Cowley, Jr., Chairman, 1983–1986; Leonard Share, Secretary 1984–1987; William Dantzler, Treasurer, 1985–1988; and Robert Shade, Program Committee Representative, 1983–1986.

### Section Symposia

It was emphasized that one of the primary functions of the scientific sections of APS is to organize and to present scientific sessions, symposia, and other programs of interest to physiologists in our area. It is hoped that members of this section would, throughout the year, send symposium suggestions to our Program Committee Representative, presently Dr. Robert Shade (University of Texas, San Antonio). The symposium recommended for the Spring FASEB Meeting of 1987 will be chaired by Dr. Kim Johnson and entitled "Central Mechanisms in the Control of Body Fluids."

(*Continued on p. 60*)

## Society Sections

**Cardiovascular**
L. B. Rowell, Chair (1987)
N. R. Alpert, Secretary (1987)
J. S. Janicki, Cardiac Mechanics Subsection (1987)
D. N. Granger, Splanchnic Circulation Subsection (1987)
A. W. Cowley, Jr., Program Advisory Committee (1987)
J. W. Downey, ex officio, Program Advisory Committee (1987)
L. B. Rowell, Section Advisory Committee (1987)

**Cell and General Physiology**
J. Lieberman, Chair (1987)
C. Pace, Secretary (1989)
A. V. Somlyo, Councillor (1988)
L. Reuss, Councillor (1989)
P. J. Deweer, Program Advisory Committee (1987)
L. Reuss, Section Advisory Committee (1989)

**Comparative Physiology**
D. C. Jackson, Chair (1987)
R. B. Reeves, Past Chair (1986)
W. K. Milsom, Secretary (1987)
R. Fedde, Councillor (1987)
L. Crawshaw, Program Advisory Committee (1987)
R. B. Reeves, Section Advisory Committee (1987)

**Endocrinology and Metabolism**
S. Leeman, Chair (1987)
C. Desjardins, Secretary (1989)
J. Gerich, Councillor (1988)
L. S. Jefferson (1988)
G. A. Hedge, Program Advisory Committee (1987)
L. S. Jefferson, Section Advisory Committee (1989)

**Environmental, Thermal and Exercise Physiology**
D. Robertshaw, Chair (1989)
M. J. Kluger, Councillor (1988)
D. Robertshaw, Program Advisory and Section Advisory Committees (1989)

**Gastrointestinal**
H. J. Cooke, Chair (1987)
H. Ormsbee, Secretary (1989)
J. Williams, Councillor (1987)
N. Weisbrodt, Councillor (1987)
L. Lichtenberger, Program Advisory Committee (1987)
N. Weisbrodt, Section Advisory Committee (1987)

**History of Physiology**
J. B West, Chair (1987)
T. Appel, Secretary (Indefinite)
R. H. Kellogg, Member-at-Large (1987)
N. C. Staub, Program Advisory and Section Advisory Committees (1987)

**Nervous System**
J. Trubatch, Chair (1987)
E. Satinoff, Steering Committee (1986)
J. Lipton, Steering Committee (1986)
J. C. Houk, Steering Committee (1986)
C. Edwards, Steering Committee (1987)
L. M. Mendell, Steering Committee (1987)
C. Eyzaguirre, Steering Committee (1988)
M. D. Gershon, Steering Committee (1988)
D. A. McAfee, Steering Committee (1988)
M. I. Phillips, ad hoc member
R. Lydic, ad hoc member and Program Advisory Committee-elect
J. Trubatch, Program Advisory and Section Advisory Committees (1987)

**Neural Control and Autonomic Regulation**
V. S. Bishop, Chair (1987)
P. G. Schmid, Secretary (1987)
M. P. Kaufman, Treasurer (1987)
M. I. Phillips, Program Advisory Committee (1987)
V. S. Bishop, Section Advisory Committee (1987)

**Renal Physiology**
L. P. Sullivan, Chair (1987)
W. J. Arendshorst, Secretary (1987)
E. H. Blaine, Treasurer (1987)
W. F. Boron, Program Advisory Committee (1987)
R. G. O'Neill, Program Advisory Committee Elect (1989)
L. P. Sullivan, Section Advisory Committee (1987)

**Respiratory Physiology**
J. Butler, Chair (1987)
P. Wagner, Secretary-Treasurer (1988)
R. W. Hyde, Councillor (1988)
J. R. Rodarte, Councillor (1989)
A. E. Taylor, Program Advisory Committee (1989)
J. A Nadel, Section Advisory Committee (1987)

**Teaching of Physiology**
R. Carlin, Chair (1987)
E. Rosenberg, Secretary-Treasurer (1987)
D. Bruce, Councillor (1987)
J. Michael, Program Advisory Committee (1989)
H. Modell, Section Advisory Committee (1990)

**Water and Electrolyte Homeostasis**
A. W. Cowley, Jr., Chair (1987)
L. Share, Secretary (1987)
W. Dantzler, Treasurer (1988)
L. G. Navar, Councillor (1988)
E. Blaine, Program Advisory Committee (1988)
A. W. Cowley, Jr., Section Advisory Committee (1987)

SECTION REPORTS (*Continued from p. 59*)

### Social Functions of Section

There was unanimous support at the business meeting for initiation of a social function related to the Spring FASEB Meeting. To provide for such activities, it was proposed that annual dues of $5.00 be levied on section members. We have been informed by the Society, however, that this is not permitted presently but is under consideration together with seemingly all other aspects of the Society.

### Relationship of Section with Section Advisory Committee

As representative to the Section Advisory Committee, Allen Cowley reported on the evolution of the proposed plans for strengthening of the representation of sections in the overall governance of the American Physiological Society. It has been recommended by the Section Advisory Committee that each section appoint a representative for a 3-year term to provide continuity and long-range planning within the Society. The Council of the Society is presently examining a variety of suggestions made by the long-range planning committee to deal with the details of these issues. Nonetheless, it is clear that several things will be necessary with any of the potential models that are used. First, each person will have to choose a primary affiliation for a section and be a voting member from only one section. The sections that remain as sections under this procedure will have to have a representative appointed for a 3 year term to the Section Advisory Committee. It was the feeling of the members present at the business meeting that the most appropriate way to represent the section would be to designate the present Secretary for a 3-year term: year 1 as Secretary, year 2 as Chairman (to which the Secretary is automatically elevated), and year 3 as Past-Chairman. This would mean every third Secretary would serve as our representative. A final recommendation related to this issue will be made in the future by the Steering Committee of this section.

### Section Affiliation

If the Section on Water and Electrolyte Homeostasis is to continue as a section of the American Physiological Society, at least 100 of the nearly 500 members who originally became affiliated with this section will be required to designate this section as their primary affiliation for future governance of the Society. Many members of this section are also members of other sections of the Society, and it appears at this time that a choice will have to be made. To ascertain the future of this section, a ballot will also be used to poll our membership to determine how many members would desire primary affiliation with this section.

Allen W. Cowley, Jr., Chairman

# Section Five-Year Reports

## Environmental, Thermal, and Exercise Physiology

During the past 5 years under the leadership of Drs. Elizondo and Gisolfi, the section has been active in promoting the diversity of disciplines represented in this section. In this respect, the section has sponsored symposia and themes for both the Fall and Spring Meetings. In addition, the Section has organized the Temperature Regulation Dinner and the Exercise Mixer at the Spring (FASEB) Meetings. These have traditionally been held on the Tuesday and Wednesday evenings, respectively. Attendance has been approximately 80–100 at each of these events. The section therefore has been active and continues to promote the academic interests of the section members.

### Officers

In 1984 the section elected one representative to serve on both the Program Advisory Committee (PAC) and the Section Advisory Committee (SAC). In addition, a steering committee of three members was also selected: one member to serve for 3 years, one for 2 years, and one for 1 year. The PAC/SAC representative originally selected was Dr. Loring Rowell. Members of the Steering Committee were Dr. David Robertshaw (3 years), Dr. Matthew Kluger (2 years), and Dr. Peter Raven (1 year). However, Dr. Rowell already had become an officer of the Cardiovascular Section and could not accept the position since one person cannot serve two sections. Dr. Robertshaw, as the senior member of the Steering Committee, then moved into his position as PAC/SAC representative, and as of now no further election has taken place for replacement on the Steering Committee.

Thus, by default, the 3-year appointee to the Steering Committee is also the PAC/SAC representative. It so happens that Dr. Robertshaw was also asked to take over the organization of Temperature Regulation Dinner from Dr. Ethan Nadel, who had organized it for 10 years. The transfer of responsibility for the Temperature Regulation dinner was carried out separately and independently, and thus the development of an autocracy within the section is purely fortuitous!

**Other Activities**

The Temperature Regulation Dinner is the main focus of activity of the section at which an invited speaker makes a scientific presentation. At the same event, an award is given, "The Young Investigator Prize," a $200.00 check for the graduate student who has presented the best paper at the previous year's meeting or the current meeting. The winners from 1980 have been 1980, Martha O'Donnell, University of California, Davis; 1981; Richard Moalli, Brown University; 1982, Kelvin J. A. Davies, University of California, Berkeley; 1983, Nancy Rousch, Mayo Medical School; 1984, Dennis Grahn, Portland State University; and 1985, Karen Wilson, University of Florida.

The nature of our discipline is such that we have interaction with many of the other components of physiology, and members of the section whose interest is primarily thermoregulation have found that it has become increasingly difficult to obtain a peer review of their grant proposals. NIH was appraised of this problem and requested names of individuals who could serve on various study sections and would thus be able to provide an adequate peer review. A letter was circulated to members of the section and names solicited. From the list of names, certain individuals are being asked whether they would allow their names to be released to NIH for consideration as potential members of NIH study sections, particularly those related to thermoregulation and exercise physiology.

In conclusion, the section continues to thrive and reflect the progress and development taking place in the area of environmental thermal and exercise physiology.

D. Robertshaw, Representative
Section Advisory and Program Advisory Committees

## Nervous System

The FASEB meeting and The APS ceased to be the central focus for neurophysiologists particularly and neuroscientists generally with the formation of the Society for Neuroscience in 1970. Although the current membership of the section is over 900, based on those APS members listing the nervous system as their primary or secondary interest, the latest survey requesting members to list their choice of section affiliation yielded between 200 and 300 responses for the Section on the Nervous System. This is consistent with the number of responses we have gotten each year in our general election for Steering Committee.

David Carpenter was chair of the section's Steering Committee in the late 1970s, followed by Richard Orkand in 1980. Richard left to go on sabbatical in 1981 and asked me to take over his duties. When he did not return the following year, I was officially appointed chair of the section and subsequently reelected for a second term in 1984.

By the early 1980s the section had degenerated to such a point that only two or three people (out of 9 or 10) attended Steering Committee meetings, even when held in conjunction with the Society for Neuroscience Meeting, and symposia and slide sessions devoted primarily to neurobiological topics attracted an audience of three or four in addition to the participants. The nervous system group had to decide whether to continue to participate in APS meetings or to give up participation entirely. I conducted an informal pole of chairs of physiology departments who were neuroscientists and others who had been active in APS for many years; the conclusion was that it would be bad for both APS and the neuroscientists to sever their tenuous connections. In 1982 Don Humphrey, Jim Blankenship, and Ian Phillips were elected to the Steering Committee, and all the members began to work for the revitalization of the section.

The Fall 1982 APS Meeting was in San Diego with the Physiological Society of Mexico. Although the Section on the Nervous System usually does not participate in the fall meetings, since the Southern California region is replete with neuroscientists, the section suggested two symposia: one chaired by Benzanilla and the other by Arechiga, both of which were excellent and exceptionally well attended. In addition, Nick Spitzer and Ted Bullock hosted a reception for neuroscientists at University of California, San Diego, and APS kindly provided transportation between the meeting site and the campus.

(*Continued on p. 62*)

**Epithelial Transport Group**
R. A. Frizzell, Chair (1988)
P. Aronson, Steering Committee (1988)
D. Dawson, Steering Committee (1988)
E. Wright, Steering Committee (1988)
R. A. Frizzell, Program Advisory Committee and Section Advisory Committee (1988)

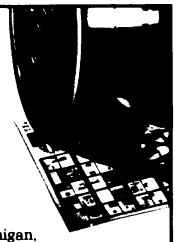
**MYOBIO Group**
M. Siegman, Chair
R. S. Eisenberg, Steering Committee
R. L. Moss, Steering Committee
J. A. Rall, Steering Committee
F. S. Fay, Steering Committee
A. W. Jones, Steering Committee
A. Fabiato, Steering Committee
M. Lieberman, Steering Committee
R. J. Solaro, Steering Committee
M. Siegman, Program Advisory and Section Advisory Committees

## News in Physiological Sciences

In 1985 the Society entered into an agreement with the International Union of Physiological Sciences for the joint publication of *News In Physiological Sciences* (*NIPS*). The journal is edited by Knut Schmidt-Nielsen, who was appointed by a joint managing board made up of two representatives from APS (H. E. Morgan and J. B. West) and two from IUPS (H. Valtin and K. Thurau). APS serves as the managing publisher through the Bethesda Publications Office.

By this time you have received several copies of *NIPS*. We hope you have read them and come away with a sense of having learned something and with enjoyment. However, if the publication is to meet the needs of the members of APS, it is important that you let those responsible for the publication hear from you with suggestions for improvements. Please send your comments to the chief editor or to one of the members of the joint managing board.

**This publication is available in microform from University Microfilms International.**



Call toll-free 800-521-3044. In Michigan, Alaska and Hawaii call collect 313-761-4700. Or mail inquiry to: University Microfilms International, 300 North Zeeb Road, Ann Arbor, MI 48106.

## APS Fall Meeting Workshop

Participants in the upcoming meeting of the American Physiological Society in New Orleans (October 6–10, 1986) who are interested in the integrative study of physiological systems will be pleased to learn that daily sessions devoted to this subject will be held at the meeting.

A medical case history (Case 41-1968, *New England Journal of Medicine* 279: 819, 1968) will provide the framework for discussion. It involves problems involving electrolyte, fluid, and acid-base balance; hypothermia; cardiac arrest; and intestinal necrosis in a comatose woman suffering the consequences of untreated diabetes mellitus.

Emphasis will be placed on the elucidation of the physiological events that generate identified disease processes and on an understanding of physiological interrelationships that shed light on differences among health, illness, dying, and death.

These sessions will provide an opportunity for discussions that transcend specific problems, organ systems, or areas of specialization. Sessions will be in the form of a colloquy, a discussion, in which there are no boundaries to thought and in which any issue, from the molecular through the organismal, can be examined.

Participants in the APS meeting who would enjoy such an exploration of wide-ranging scientific problems are cordially invited to attend and to take part in the discussions. (Integrative Studies,* Dept. of Physiology and Biophysics, Albert B. Chandler Medical Center, University of Kentucky, Lexington, KY 40536-0084.)

* In association with Dr. Robert S. Alexander (Baylor College of Medicine) and Dr. Robert L. Vick (Delmar, NY).

## Irwin J. Fox (1926–1986)

I. J. died with his boots on, as Chairman of the Society's Committee on Animal Care and Experimentation, during a period of high importance of this role to the Society.

Trained under Dr. Maurice C. Visscher at the University of Minnesota, he spent his entire academic career there. His loyal and wise contributions to the Society and its objectives were of great benefit.

SECTION FIVE-YEAR REPORTS (*Continued from p. 61*)

The following year, in Chicago, Jim Houk and the chairman of pharmacology hosted a reception and poster exhibit at the Northwestern University of Medicine. The session was so well attended that the section decided to run the receptions on the convention sites for subsequent meetings, and Wednesday night, April 17th, will be the third of these social gatherings.

To combat the problem of low attendance at symposia, the section has concentrated on devising sessions in conjunction with other sections. "Update in Cardiovascular Neurobiology," a four-part symposium presented at FASEB, 1984, in St. Louis, was organized by the Nervous System, Cardiovascular, and Autonomic Control Sections (Ferrario, Brody, and Trubatch). Sponsorship by Gould Instruments not only provided funds to support the involvement of foreign physiologists (as did a Carolyn tum-Suden Travel Award) but yielded a magnificent shipboard dinner for all the participants. Gould was so impressed with this symposium that it has provided APS funds for a similar update in cardiovascular neurobiology each year at the FASEB meeting. This year's symposium on carotid body chemoreceptors chaired by Carlos Eyzaguirre is another example of the combined interests of several sections.

The section has also had some success with providing neuroscience symposia of more general interest. "Historical and Modern Perspectives in Neurophysiology" (FASEB, 1984) was cosponsored by the Centennial Committee. Robert Frank, Neuroanatomist/Historian from UCLA, discussed the history of the development of experimental equipment, while four of our members presented modern developments in the field. In this year's "Perspectives" Program, James Lipton has arranged for presentations on unresolved issues in neurobiology.

In 1985 Carlos Eyzaguirre, Mike Gershon, and Don McAfee were elected to the Steering Committee, joining Evelyn Satinoff, Jim Lipton, James Houk, Janett Trubatch, Charles Edwards, and Lorne Mendell.

For the future, the goals of the Section of the Nervous System are to continue to develop smashing symposia for the Spring Meetings, to enjoy a cocktail hour together, and to join with other physiologists in understanding how the various physiological systems work together to yield functioning organisms.

Janett Trubatch, Chairperson

## Renal

The goals of the Renal Section of APS are to foster communication among its members in order to enhance the progress of research in renal and electrolyte physiology and to advise APS on matters of interest to its members. The section attempts to achieve these goals by participating in the planning of the scientific program of APS meetings, by encouraging student participation in the meetings, and by providing a setting for informal communication among members and students. Specifically, symposia and lectures are organized for presentation at meetings of APS, awards are presented to students for the quality of their presentations, and an annual cocktail hour and banquet are held at the FASEB meeting.

The Steering Committee, consisting of the three officers and the representatives to the APS Program Advisory Committee, is responsible for management and supervision of the affairs of the section. These officers are elected to 2- and 3-year terms by the members present at the annual banquet meeting of the section.

### Officers of Renal Section

At the start of the 5-year period, the chairman, secretary, and treasurer were elected to 1-year terms. To provide continuity, one representative to the Program Advisory Committee (PAC) of APS was elected to a 2-year term each year. In 1983 the terms of the chairman, secretary, and treasurer were changed to 2 years. In 1985 the terms of the representatives to PAC was increased to 3 years. Now the representatives are elected such that the last 2 years of one overlap with the first two of the other.

The officers have been:

1981–1982: F. Wright, Chairman; P. Churchill, Treasurer; D. Warnock and E. Schneider, PAC representatives.

1982–1983: D. Marsh, Chairman; P. Churchill, Secretary; T. Northrup, Treasurer; D. Warnock and P. Aronson, PAC representatives.

1983–1984: P. Churchill, Chairman; E. Schneider, Secretary; L. Sullivan, Treasurer; P. Aronson and G. Navar, PAC representatives.

1984–1985: P. Churchill, Chairman; E. Schneider, Secretary; L. Sullivan, Treasurer; G. Navar and W. Boron, PAC representatives.

In 1985 the following were elected to office: L. Sullivan, Chairman; W. Arendshorst, Secretary; and E. Blaine, Treasurer. W. Boron continues to serve as PAC representative.

### Sponsored Symposia and Lectures

1981 FASEB Symposia: *1)* Comparative Studies of the Control of Renal Function, chaired by F. G. Knox (*Federation Proc.* 41: 2347–2382, 1982); *2)* Regulatory Role of Calcium in the Kidney, chaired by J. C. S. Fray; and *3)* What Role do Nerves Play in Renin Release?, chaired by A. C. Barger and J. W. Manning.

1981 Fall APS Symposium: Intrinsic Control of Renal Hemodynamics, chaired by L. G. Navar (*Federation Proc.* 41: 3022–2030, 1982).

1981 Fall APS Tutorial Lectures: *1)* Salt and Water Transport by Proximal Tubule, J. A. Schafer; *2)* Regulation of the Renal Circulation by Prostaglandin-Dependent Mechanisms, chaired by J. C. McGiff; *3)* The Renin-Angiotensin System and the Brain, I. A. Reid; *4)* Developmental Renal Physiology, L. I. Kleinman; and 5) Tubular Reabsorption of Low-Molecular-Weight Proteins, E. C. Foulkes.

1982 FASEB Symposia: *1)* The Renal Concentrating Mechanism I: Basic Concepts and Data, chaired by J. L. Stephenson; *2)* The Renal Concentrating Mechanism II: Models and Experiments, chaired by C. Lechene and B. Kellogg (*Federation Proc.* 42: 2377–2405, 1983; cosponsored with the Society of Mathematical Biology); *3)* Central Nervous System Regulation of Sodium Excretion, chaired by S. L. Bealer and E. G. Schneider; *4)* Kidney and Cardiovascular Regulation, chaired by R. Berliner and V. J. Dzau (*Federation Proc.* 42: 3135–3176, 1983).

1982 Fall APS Tutorial Lectures: *1)* New Concepts of Nephron Structure, F. S. Wright; and *2)* The Role of Aldosterone, Sodium, Chloride and Potassium in Metabolic Alkalosis, N. A. Kurtzman.

1983 FASEB Symposia: *1)* Control of Glomerular Function by Intrinsic Contractile Elements, chaired by B. M. Brenner (*Federation Proc.* 42: 3025–3079, 1983); *2)* Ion Transport Processes in Apical Membranes of Epithelia, chaired by D. G. Warnock (*Federation Proc.* 43: 2473–2487, 1983; cosponsored with Epithelial Transport Section); and *3)* Ion Transport Processes in Basolateral Membranes of Epithelia, chaired by L. Reuss (*Federation Proc.* 43: 2488–2502, 1983; cosponsored with Epithelial Transport Section).

1983 Fall APS Tutorial Lecture: Comparative Physiology of the Renin-Angiotensin System, R. L. Malvin.

1984 FASEB Symposia: *1)* Structural Correlates of Transport Regulation in Renal Epithelia, chaired by J. B. Wade (*Federation Proc.* 44: 2685–2727, 1985; cosponsored with three other sections); and *2)* Regulation of Renal Phosphate Transport, chaired V. W. Dennis).

1984 Fall APS Symposia: *1)* Intrarenal Hemodynamics, chaired by J. C. Passmore; and *2)* Neural Control of Renal Function, chaired by G. F. DiBona (*Federation Proc.* 44: 2815–2850, 1985).

1985 FASEB Symposia: *1)* Physiological Role of the Renin-Angiotensin System, chaired by L. G. Navar, and *2)* Atrial Natriuretic Factors (2 sessions), chaired by H. Sonnenberg and T. Maack. (Cosponsored with Water and Electrolyte Homeostasis Section).

1985 Fall APS Symposium: Renal Functional Derangements in Hypertension, chaired by B. G. Zimmerman.

1985 Fall APS Tutorial Lectures: *1)* Control System Analysis of Mechanisms of Renal Autoregulation, L. Moore; *2)* Role of Plasma Sodium in the Control of Aldosterone Secretion, E. Schneider; *3)* Importance of the Angiotensin II Receptor as a Modulator of Aldosterone Secretion, J. Douglas; and *4)* Functional Significance of Aldosterone, D. Young (Last 3 were cosponsored with Water and Electrolyte Homeostasis Section).

### Student Awards

To foster and encourage student participation in the meetings of APS, the section presents awards to students whose papers or posters at the meetings have been judged to be outstanding. Before the meetings the members are asked to nominate their students who are presenting papers and a committee judges the presentation. An appropriate certificate and a prize of $100 are awarded at the annual dinner meeting. A partial list of winners in recent years is Pamela Carmines, Univ. of Indiana School of Medicine; Patricia King, Brown University; V. Pahronmphetcharat, Louisiana State University; Mu En lee, University of California at San Francisco; and Eric Pierce, University of Michigan.

### Annual Dinner Meetings

The Renal Section holds a dinner meeting each year at FASEB. The ticket price for students is partially underwritten by donations obtained from pharmaceutical companies. The awards for students also comes from this source. The speakers at this meeting for the last 5 years have been Richard Malvin, Jared Grantham, Heinz Valtin, William Dantzler, and Frank Knox. The attendance at these meetings has ranged from 85 to 120.

Lawrence Sullivan, Chairman

## Scholander Award

The Scholander Award is presented annually for the best abstract and presentation in comparative physiology by a young investigator at the Fall Meeting of APS. The award for 1986 will be accompanied by a cash award of $100 and a certificate from APS.

Applicants for the Scholander Award must *1)* be first author on the abstract, *2)* present the study in a comparative physiology slide or poster sessions at the Fall APS Meeting, *3)* be not more than 5 years past their highest degree, and *4)* be a member of the APS (any category). Applicants for the award should send a copy of their abstract for the meeting to the Chairman of the Comparative Physiology Section, APS, with a note indicating their intent.

Applicants will be judged by a five-member panel composed of at least two members of the Comparative Physiology Section Executive, the chairman of the slide or poster session, and two senior comparative physiologists selected by the executive.

Members of the APS and Friends of Professor P. F. Scholander are encouraged to contribute to the Scholander Award Fund. Contributions are tax deductible, and checks should be made payable to APS "Scholander Award Fund". The Scholander Award for 1986 will be presented to the winning candidate at a fund-raising dinner to be held in support of the award at the meeting in New Orleans. All members of the section are encouraged to attend.

## Julius Comroe Memorial Symposium

The Julius Comroe Memorial Symposium, "Receptors and Reflexes in Breathing," will be held at the University of Pennsylvania, Philadelphia. New dates are March 26–28, 1987. Sessions include Peripheral Chemoreceptors and Chemoreflexes, Central Chemoreceptors and Chemoreflexes, Pulmonary Receptors and Reflexes, and Central Mechanisms and Integration. For further information, contact Dr. S. Lahiri, Dept. of Physiology, University of Pennsylvania School of Medicine, Richards Bldg. A201, Philadelphia, PA 19103-6085.

# Honorary Members

Since the establishment of Honorary Membership in the American Physiological Society, the following distinguished scientists have been elected. The year of their election is indicated. Masao Ito and John R. Vane are our most recent distinguished Honorary Members.

E. D. Adrian†, Cambridge, UK (1946)
J. Barcroft†, Cambridge, UK (1946)
E. Braun-Menendez†, Buenos Aires, Argentina (1959)
F. Bremer†, Brussels, Belgium (1950)
A. Dastre†, Paris, France (1904)
P. Dejours, Strasbourg, France (1981)
J. C. Eccles, Canberra, Australia (1952)
T. W. Engelmann†, Berlin, Germany (1904)
D. P. Feng, Shanghai, People's Rep. of China (1983)
B. Folkow, Goteborg, Sweden (1982)
R. Granit, Stockholm, Sweden (1963)
R. A. Gregory, Liverpool, UK (1981)
E. Gutman†, Prague, Czechoslovakia (1971)
O. Hammarsten†, Uppsala, Sweden (1907)
W. R. Hess†, Zurich, Switzerland (1950)
A. V. Hill†, London, UK (1946)
A. L. Hodgkin, Cambridge, UK (1952)
F. Hofmeister†, Strassburg, Germany (1904)
B. A. Houssay†, Buenos Aires, Argentina (1941)
A. Hurtado†, Lima, Peru (1959)
A. Huxley, London, UK (1981)
H. E. Huxley, Cambridge, UK (1981)
M. Ito, Tokyo, Japan (1986)
G. Kato†, Tokyo, Japan (1965)
B. Katz, London, UK (1985)
A. Krogh†, Copenhagen, Denmark (1946)
Y. Kuno†, Tokyo, Japan (1959)
J. N. Langley†, Cambridge, UK (1904)
L. Lapique†, Paris, France (1946)
G. Liljestrand†, Stockholm, Sweden (1950)
C. Monge†, Lima, Peru (1952)
G. Morruzzi, Pisa, Italy (1959)
L. A. Orbeli†, Leningrad, USSR (1946)
I. R. Pavlov†, Russia (1904)
E. Pflüger†, Bonn, Germany (1907)
W. T. Porter†, Dover, MA (1948)
F. J. W. Roughton†, Cambridge, UK (1957)
E. Sharpey-Schaefer†, UK (1912)
C. Sherrington†, Oxford, UK (1904)
E. T. A. Teorell, Uppsala, Sweden (1985)
K. J. Ullrich, Frankfurt/Main, FRG (1985)
H. H. Ussing, Copenhagen, Denmark (1950)
K. von Frisch†, Munich, Germany (1952)
Sir J. R. Vane, London, UK (1986)
C. von Voit†, Munich, Germany (1970)
H. H. Weber†, Heidelberg, Germany (1959)

† Deceased.

## Masao Ito

Masao Ito was born at Nagoya, Japan, in 1928. He studied medicine at the University of Tokyo, graduating in 1953. In 1954, his career of neurophysiology began as an assistant professor in Kumamoto University and then as assistant professor in the University of Tokyo. He joined Sir John Eccles in Canberra from 1959 to 1962. He became associate in 1963, professor in 1970, and Dean of the Medical Faculty of the University of Tokyo in 1986. Since 1978 Dr. Ito has been President-Secretary of the Japanese Physiological Society; since 1982, President of the Japan Neuroscience Society. He became President of IBRO in 1980 and a council member of IUPS in 1982.

Dr. Ito's doctoral thesis was on electrical activity of dorsal root ganglion cells. In Canberra, he studied ionic mechanisms of inhibitory synapses, multiexponential membrane properties, and summation of afterhyperpolarization in spinal motoneurons. After returning to Tokyo, Dr. Ito worked continuously on the cerebellum, first for identification of Purkinje cells as exclusively inhibitory neurons and of $\gamma$-aminobutyric acid as neurotransmitter of Purkinje cells and then for dissection of neuronal connections of the cerebellar flocculus with the vestibuloocular reflex, leading to proposal of the hypothesis that the flocculus is the site of adaptive control of the vesitbuloocular reflex. His recent efforts have been directed to characterize the long-term depression of synaptic transmission in the cerebellar cortex as a memory process for motor adaptation and learning.

The author of over 120 articles, Dr. Ito has published ***The Cerebellum as a Neuronal Machine, Physiology of Neurons, and Blueprint of the Brain.*** His most recent book, ***The Cerebellum and Neural Control,*** is highly regarded and is remarkable for its clarity and breadth. In 1981 Dr. Ito received the Fujiwara-Prize and was awarded the Imperial Prize and Academic Prize from the Japan Academy in 1986.

## John R. Vane

I was born in Tardebigg, Worcestershire, in 1927. At the age of 12, my parents gave me a chemistry set for Christmas, and experimentation soon became a consuming passion in my life. At first, I was able to use a Bunsen burner attached to my mother's gas stove, but the use of the kitchen as a laboratory came to an abrupt end when a minor explosion involving hydrogen sulphide spattered the newly painted decor and changed the color from blue to dirty green! Shortly afterwards, my father erected a wooden shed for me in the garden, fitted with bench, gas, and water. This became my first real laboratory, and my chemical experimentation rapidly expanded into new fields.

At high school I progressed through the pure science, and in 1944 I moved to the University of Birmingham to study chemistry. However, the enthusiasm with which I had approached experimentation in chemistry in the garden shed was soon dampened, for at the university experimentation was nonexistent. The only unknown in the practical class was the percent yield in the chemical synthesis involved. At this stage, I began to realize that my interest lay not in chemistry but more in experimentation. Thus, when Maurice Stacey, the Professor of Chemistry, asked me what I wanted to do when I graduated, I said "anything but chemistry." Stacey then told me that he had received a letter that morning from Professor Harold Burn in Oxford asking whether he could recommend another young chemist to go to Oxford to be trained in pharmacology. Without hesitation I grasped the opportunity and immediately went to the library to find our what pharmacology was all about! That brief exchange with Stacey reshaped my whole career.

I went to Burn's department in 1946. I had no biological training of any sort and very little motivation. I found inspiration in working with him and caught his enthusiasm for pharmacology. His laboratory was the most active and important center for pharmacological research in the UK and the main school for training of young pharmacologists. It was his energy and inspiration that set my career into one of adventure in the fields of bioassay and pharmacology. It was Burn who reinforced for me the essence of experimentation and that is never to ignore the unusual.

(*Continued on p. 65*)

## USA-USSR Physiologist Exchange Program

At the recent meeting of the American Physiological Society, the Council had the pleasure of playing host to Professor Alexi M. Ivanitsky, Scientific Secretary of Pavlov's All-Union Physiological Society. Professor Ivantisky's visit is a continuation of the exchange initiated by the visits of Drs. John B. West and Orr E. Reynolds [*The Physiologist* 28(6): 463, 1985] to the Soviet Union during the summer of 1985. During their trip, Drs. West and Reynolds met with Professor Oleg Gazenko, Dr. Ivanitsky, and others. From these visits, it became clear that they were very interested in promoting a collaboration between the two groups and obtaining information about the American Physiological Society, its governance, and types of meetings. This was brought up to Council at its Fall Meeting in Niagara Falls, followed by an invitation to Professor Gazenko to attend the Spring Meeting. Professor Gippenritter will be a guest at the APS Fall meeting in New Orleans. Dr. West personally thinks it is a tremendous idea to develop an exchange between the two groups.

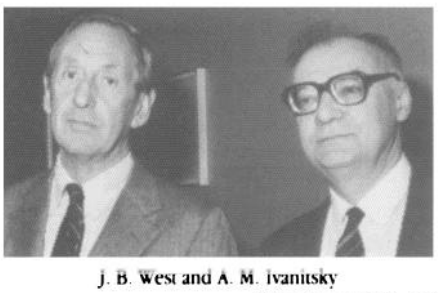
Professor Ivanitsky delivered a letter from the President of the Society, Professor O. Gazenko, in which he expressed his desire that Professor Ivanitsky's visit would be a continuum of those direct contacts that were established between the two societies last year after a visit to the USSR by Drs. West and Reynolds.

*Left to right:* M. Frank, H. V. Sparks, Jr., A. M. Ivanitsky

As background, Professor Ivanitsky said that his society was founded in 1917 by Pavlov, the first Noble Prize winner in physiology, as Pavlov's All-Union Physiological Society. It has about 7,000 members and in its short history has achieved some good results. It has 100 regional departments in all big towns in which there are physiologists in medical institutions and universities. They have 14 republican societies. The Soviet Union consists of 15 republics, but Russia does not have its own society because it is too large. There are 10 special regions that join regional and local district societies. An All-Union Physiological Congress is held in the fall and attended by approximately 1,500 members. It is dedicated to all topics on developments of physiology in the field in the last 3–4 years. During the congress, there is the election of a new staff council, consisting of about 150 members. It elects a working staff of about 40 members. The presidency has no time limitation, and President Gazenko has been President since 1983. There are seven physiological magazines published by the Academy of Science and the Ministry of Health. The society publishes information material quarterly devoted to their social life, conferences, and other activities.

"Why am I here?" asked Professor Ivanitsky. He said, "The fact that I am here is more important than what I can say." It is a great desire of his society to have mutual contacts and understanding with foreign physiologists and it is considered especially important to have contact and interrelationship with APS. His society was very pleased to be invited to this meeting. Visits are not easy since his society is not separate but is included in the system of the Academy of Science of the USSR. Their financial sources are limited. After the invitation from APS, Professor Gazenko went to the academy, and after extensive consultation obtained approval to come.

It is the hope and desire of his society to have an exchange of one or two physiologists to attend their respective society



J. B. West and A. M. Ivanitsky

(*Continued on p. 78*)

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**HONORARY MEMBERS** (*Continued from p. 64*)

After qualifying for a B.Sc. in pharmacology, I spent a few months in Sheffield University as a research worker in the pharmacology department but then went back to Oxford to the Nuffield Institute for Medical Research in order to study for a D. Phil. with Dr. Geoffrey Dawes. In 1951 I was awarded the Stothert Research Fellowship of The Royal Society, and this enabled me to complete my doctorate in 1953.

In 1953 at the invitation of Dr. Arnold Welch I joined the Department of Pharmacology at Yale University as Assistant Professor in Pharmacology. That was a lively and bustling department, but after 2 years we returned to the UK, where I started work with Professor W. D. M. Paton at the Institute of Basic Medical Sciences of the University of London in the Royal College of Surgeons of England. This was an unusual department, for the teaching was only for graduates and was not time consuming, thus offering plenty of time for research. I stayed there for 18 years, progressing from senior lecturer to reader to Professor of Experimental Pharmacology. From 1961 to 1973 Professor G. V. R. Born, a close friend from my Oxford days, was chairman of the department and we enjoyed a strong symbiotic relationship, each maintaining an active group of graduate students and research workers. Interestingly, our fields of research endeavour (platelets and prostaglandins) only coalesced in a significant way after we had both moved on.

It was here that I developed, together with my group, the cascade superfusion bioassay technique for measurement of, dynamically and instantaneously, the release and fate of vasoactive hormones in the circulation or in the perfusion fluid of isolated organs. In the mid-1960s, our attention was focused on prostaglandins, leading in 1971 to the forging of the link between aspirin and the prostaglandins.

In 1973 I was offered the position of Group Research and Development Director for The Wellcome Foundation. In making my decision, I was conscious that Henry Wellcome, 70 years before, had recruited Henry Dale to work in (and soon to direct) the Wellcome Physiological Research Laboratories, the forerunners of the present Research and Development Directorate. When Henry Dale, then at Cambridge, first received the offer from Wellcome, he hesitated over accepting it. "Friends to whom I mentioned this approach" he said, "were almost unanimous in advising me to have nothing to do with it. I should be selling my scientific soul for a mess of commercial potage." Nevertheless, he accepted and had no regrets. I also found among a few of my friends a resistance to the idea of me entering into industrial science. It was as if to say that good science can only be promulgated in academia. Those friends were wrong; like Dale I accepted and had no regrets. I took with me from the Royal College of Surgeons a nucleus of colleagues, and this has expanded over the last few years into a prostaglandin research department under the leadership of Dr. Salvador Moncada. It was in this department that prostacyclin was discovered and its pharmacology developed.

# American Physiological Society
# Centennial Meeting
# Washington, DC
# March 29–April 3, 1987

Nearly a century ago, at a time when there existed only a handful of physiological laboratories in America, the organizational meeting of the American Physiological Society was held. On December 30, 1887, in New York in the Physiological Laboratory of the College of Physicians and Surgeons, Columbia University, 17 men attended and 28 were named charter members of the new society. The APS Centennial medallion honors five men who have long been considered the founders of the Society. Three of them, Henry Pickering Bowditch, S. Weir Mitchell, and Henry Newell Martin, were signers of the original letter of invitation to attend the organizational meeting. Two others, Russell H. Chittenden and John Green Curtis, also played prominent roles in the founding and early history of the Society.

To commemorate the founding of the American Physiological Society and "A Century of Progress in Physiology," the Society is planning its Centennial Celebration for March 29–April 3, 1987, in conjunction with the FASEB meeting in Washington, DC.

The week has been designated as "Founders Week" in honor of the founders of the Society. At the same time, FASEB will be celebrating its 75th Birthday. Provisions have been made by FASEB for the American Physiological Society to organize the themes for the meeting. The overall plan is not only to take full account of the start and evolution of the Society but also to combine the traditional FASEB "state-of-the-art" approach with a look ahead. In essence, this unique opportunity will be exploited in a most unusual way.

To help in this large effort, 25 distinguished physiologists from abroad have been invited to participate in the program. This is in addition to the many distinguished American physiologists who will be actively participating in the meeting. Symposia, exhibitions, and plenary sessions are planned to deal with the frontiers of the physiological sciences. In each instance, a Janus-like approach will be adopted: each timely topic will be portrayed against a historical background with full regard for its future prospects.

In addition to the scientific meetings, the proceedings will include an opening reception for members of the American Physiological Society and FASEB-member societies. The week-long celebration will close on Friday, April 3. A special reception and closing lecture for members of APS is scheduled at the National Academy of Sciences on Thursday, April 2. During the week, special events will be available for participants, including an evening at the Kennedy Center for the Performing Arts and tours of Washington landmarks.

## Plenary Lecturers

**A.M.**

**David Baltimore**, Whitehead Institute for Biomedical Research, Cambridge, MA
Developmental Regulation of Mammalian Genes

**Hector F. DeLuca**, University of Wisconsin, Madison, WI
The Vitamin D Story: A Success of Basic Science in the Treatment of Disease

**Phillip Leder**, Harvard Medical School, Boston, MA
Misplacing Oncogenes: Studies Using Transgenic Mice

**Sir John Vane**, St. Bartholomew's Hospital Medical College, London, UK
Inflammation and the Mechanism of Anti-Inflammatory Drugs

**P.M.**

**Floyd E. Bloom**, Scripps Research Institute, La Jolla, CA
Neurotransmitters: Past, Present and Future Directions

**Roger Guillemin**, Salk Institute, San Diego, CA
Control of Pituitary Functions: One Hundred Years of Progress

**Solomon H. Snyder**, Johns Hopkins School of Medicine, Baltimore, MD
Neural Receptors

## APS-Sponsored Symposia

**Molecular Biology in Physiology**
*Organizer:* Shu Chien

**Sleep-Dependent Changes in Homeostasis**
*Organizer:* Ralph Lydic

**Control Strategies in Physiological Systems**
*Organizer:* James Houk

**From Conduction of the Nerve Impulse to Ionic Channels Via Sodium Conductance**
*Organizer:* Robert Eisenberg

**Central Mechanisms Controlling Body Fluid Balance**
*Organizer:* A. K. Johnson

**Vasopressin and Fluid Balance**
*Organizer:* David Ramsay

**Cellular Mechanisms of Mesangial Cell Contraction**
*Organizer:* Detlef Schlondorf

**Regulation of Renal Transport Systems**
*Organizer:* David Warnock

**New Roles for Oxytocin**
*Organizers:* Willis Samson and Daniel Gibbs

**Cardiopulmonary-Neuroendocrine Interactions**
*Organizer:* Hershell Raff

**Autonomic Control of the Peripheral Circulation in Humans**
*Organizer:* Larry Rowell

**The Capillary Functions: Historical Perspectives for Future Directions**
*Organizer:* Aubrey Taylor

**Role of Oxygen-Free Radicals in Myocardial Ischemia and Infarction**
*Organizer:* Robert Kloner

**Cardiovascular Responses to Chronic Portal Hypertension**
*Organizer:* Neil Granger

**Endogenous Antipyretics**
*Organizer:* Matthew Kluger

**Body Fluid and Electrolyte Distribution During Thermal Stress**
*Organizer:* Reynaldo Elizondo

**Macromolecular Uptake and Transport in Epithelia**
*Organizer:* Martin Neutra

**Role of Food in Regulation of Satiety**
*Organizer:* Paul McHugh

**Skeletal Muscle Physiology: An Update and New Directions**
*Organizer:* Robert Eisenberg
**Smooth Muscle: From Membrane to Crossbridges**
*Organizer:* Marion Siegman
**The Five Founders of APS**
*Organizer:* Daniel Gilbert
**Control of the Pulmonary Circulation**
*Organizer:* Alfred P. Fishman
**Lung Growth and Development**
*Organizer:* Jerome Brody
**The Basis of Micromechanical Behavior of the Lung**
*Organizer:* Frederick Hoppin
**Approaches to the Teaching of Problem-Solving in Physiology**
*Organizers:* Joel Michael and Harold Modell
**Frontiers of Technology for Physiologists**
*Organizer:* Andrew Somlyo

## Centennial Guests

**Emilio Agostini**, University of Milan, Italy
**Anthony Angel**, The University, Sheffield, UK
**Knut Aukland**, University of Bergen, Norway
**Christian Crone**, University of Copenhagen, Denmark
**Pierre Dejours**, Centre National de la Recherche Scientifique, Strasbourg, France
**T. P. Feng**, Shanghai Institute of Physiology, Peoples Republic of China
**Björn Folkow**, University of Göteborg, Sweden
**Oleg G. Gazenko**, Institute of Biomedical Problems, Moscow, USSR (tentative)
**Sir Andrew F. Huxley**, Trinity College, Cambridge, UK
**Susan D. Iversen**, Merck, Sharpe & Dohme, Essex, UK
**Dora Jassik-Gerschenfeld**, Université Pierre et Marie Curie, Paris, France
**Kjell Johansen**, University of Aarhus, Denmark
**Sir Bernard Katz**, University College, London, UK
**Paul I. Korner**, Baker Medical Research Institute, Prahran, Victoria, Australia
**Rita Levi-Montalcini**, Laboratorio di Biologia Cellulare, Rome, Italy
**Anthony D. C. MacKnight**, University of Otago Medical School, Dunedin, New Zealand
**Carlos Monge**, Universidad Peruana Cayetano Heredia, Lima, Peru
**Johannes Piiper**, Max-Planck-Institut für experimentelle Medizin, Gottingen, West Germany
**Berry Pinshow**, Ben-Gurion University of the Negev, Sede-Boqer, Israel
**Irene I. Schulz**, Max-Planck Institut für Biophysik, Frankfurt, West Germany
**Andrzej Trzebski**, Institute of Physiological Sciences, Warsaw, Poland
**Karl J. Ullrich**, Max-Planck-Institut für Biophysik, Frankfurt, West Germany
**Sir John Vane**, St. Bartholomew's Hospital Medical College, London, UK
**Ewald R. Weibel**, Universität Bern, Switzerland
**John G. Widdicombe**, St. George's Hospital Medical School, London, UK

**Abstract deadline November 19, 1986.**
**Information: APS Centennial Meetings Office, 9650 Rockville Pike, Bethesda, MD 20814. (301)530-7010.**


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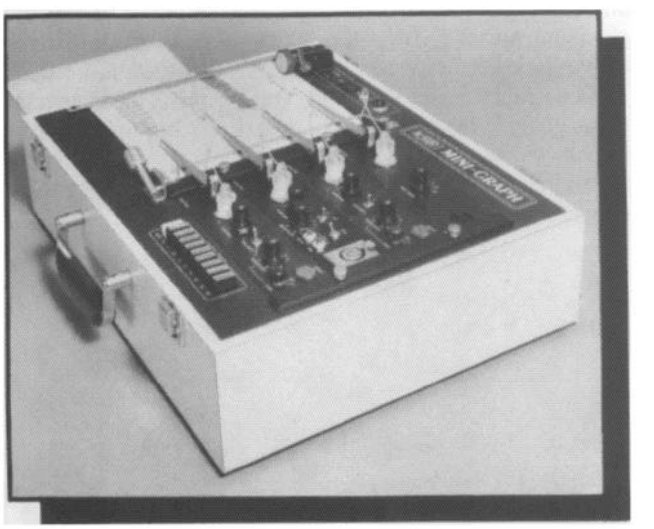

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# News from Senior Physiologists

## Letters to Edward F. Adolph:

**Nicholas S. Assali** is retiring this year from UCLA after a 40-year research career in the field of perinatal research. In his retirement he plans to write a new edition to his three volumes on Pathophysiology of Gestational Disorders and to collaborate with his oldest son, a professor of philosophy, on a book entitled *Philosophy of Sex*. The subject has interested him since the early forties, when he was a doctor for prostitutes in Brazil. He advises younger colleagues to "please take some time off from reading medical books and journals, and pick up a book of philosophy." His autobiography, *A Doctor's Life*, described in an enclosed review as a story "that has the excitement of a new *Arrowsmith*," was published in 1980.

**Charles G. Wilber** is retiring this year from the Department of Zoology of Colorado State University but will be able to retain a laboratory/office. He plans to write a monograph on theoretical and practical aspects of the biophysics of wound formation from firearms, to do further work on organic phosphate poisoning, and to organize a session addressed primarily to biomedical scientists on problems of professional ethics for the 1987 meeting of American Academy of Forensic Sciences. Each summer he and his wife go back to Woods Hole, where he has been "playing around" with allometric growth in selected invertebrate species. He urges younger colleagues to be "incurable optimists" and also to fight vigorously to maintain the practice of academic tenure, which is the mechanism that ensures academic freedom.

**Charles E. Hall**, University of Texas at Galveston, writes that he is doing much as he has always done: investigating various aspects of the endocrine and cardiovascular systems and in general making life difficult for the laboratory rat. He and his wife's interest in wildlife photography continues undiminished, and in the past 5 years they have made expeditions to Kenya, Australia, Costa Rica, and Venezuela in pursuit of that hobby. This summer they plan to do Alaska, and next winter take in Surinam.

## Letters to Arthur B. Otis:

**Charles C. Hassett** writes, that since his retirement in 1975 from his position of Chief of the Experimental Medicine Branch, Biomedical Laboratory, USA Medical Research at Edgewood Arsenal, he has done some consulting on special projects in toxicology for NIOSH and NRC. He is now fully retired. He and his wife spend summers at their house in Woods Hole.

**Herbert R. Catchpole**, who has recently celebrated his 80th birthday, writes from Ankara that he and Robin Miller-Catchpole are currently enjoying travel and archaeological interests in central and eastern Turkey. He is still teaching histology and pathology.

**Donald F. Proctor**, retired from the faculty of the Johns Hopkins School of Hygiene and Public Health, writes, "On the whole, I'm still having a hell of a good time and keeping busy at things I want to do." He is working on his *History of Breathing Physiology*, doing research on the role of upper respiratory muscles in stabilization of the airway, wood carving, singing a little, and enjoying his good fortune in his wife, two children, and three lovely grandchildren.

**James Irving**, retired from the Harvard School of Dental Medicine and from NIH, writes that at the age of 84 the editing of the *Archives of Oral Biology* represents his sole professional activity. His chief interest is in reading, especially about the Civil War.

## Letters to Ewald E. Selkurt:

**Sydney M. Friedman** reports that he is running an active laboratory at the University of British Columbia and "without academic responsibilities beyond the occa-

(*Continued on p. 74*)

## G. Edgar Folk, Jr. Senior Physiologist Fund

The American Physiological Society is pleased to announce the establishment of the G. Edgar Folk, Jr. Senior Physiologist Fund.

On behalf of the family and friends, Dr. Frank presented Dr. Folk with a plaque inscribed "The American Physiological Society presents to G. Edgar Folk, Jr., at its annual meeting on April 16, 1986, this award in commemoration of the initiation of the G. Edgar Folk, Jr. Senior Physiologist Fund and in recognition to distinguished service to the Society and to the science of physiology."

In thanking him, Dr. Folk said, "This must be the best-kept secret in all of the midwest. Last night I was informed, you will have to go up to the podium tomorrow at the Business meeting, and I was told why. I shall be very busy thanking former graduate students, associates in my laboratory, and visiting professors who have done this wonderful thing. You have to get to be a fossil to have this lovely thing happen. I could easily prove that I deserve being fossilized. My studies go back to the time when there were two neurohumors and some people did not believe they existed then. Do you remember the talk about the Spark boys and the Soup boys? I go back to the time of G. H. Parker, who first began such conversations. He worked with Cannon, and there was a great deal of debate as to whether they existed. The other day, I read there are 54 neurohumors in the brain. This represents this period of fossilization. I shall go now and attempt to thank these wonderful people."

Inquiries concerning the G. Edgar Folk, Jr. Senior Physiologist Fund should be made to Martin Frank, Executive Secretary-Treasurer, APS.

H. E. Morgan, G. E. Folk, Jr., and M. Frank

## Standing Committees

### APS Council
F. G. Knox, President
H. E. Morgan, Past President
H. V. Sparks, Jr., President-Elect
M. Frank, Executive Secretary-Treasurer
S. Chien, Councillor
J. A. Nadel, Councillor
N. C. Staub, Councillor
A. E. Taylor, Councillor

### Society Standing Committees

**Animal Care and Experimentation**
D. J. Ramsay, Chair (1989)
J. F. Amend (1987)
J. H. U. Brown (1987)
T. N. Pullman (1987)
L. Ramazzotto (1989)
I. H. Zucker, (1988)
N. B. Marshall, ex officio (1988)
W. M. Samuels, ex officio

**Career Opportunities in Physiology**
R. J. Traystman, Chair (1987)
C. M. Gregg (1988)
S. A. Nunneley (1989)
D. M. MacCanon (1988)
J. T. Reeves (1989)
C E. Vreim (1987)
R. C. Webb (1988)

**Centennial Celebration**
A. P. Fishman, Chair
O. E. Reynolds, Task Force Director
P. A. Chevalier
J. S. Cowan
D. L. Gilbert
R. J. T. Joy
R. H. Kellogg
L. L. Langley
S. Ochs
M. C. Shelesnyak
H. V. Sparks, Jr.
N. C. Staub
J. C. Johnson, ex officio
M. Frank, ex officio

***Steering Committee***
A. P. Fishman, Chair
H. E. Morgan
H. V. Sparks, Jr.
N. C. Staub
J. B. West

**Committee on Committees**
N. C. Staub, Chair (1989)
K. H. Berecek (1989)
M. J. Fregly (1988)
W. H. Dantzler (1987)
J. E. Greenleaf (1987)
C. L. Seidel (1989)
J. Van Liew (1989)

**R. G. Daggs Award**
B. Schmidt-Nielsen, Chair (1987)
R. G. Berne (1989)
F. J. Haddy (1988)

**Education**
J. A. Spitzer, Chair (1987)
F. L. Abel (1988)
J. C. Fray (1989)
H. G. Hempling (1987)
J. T. Herlihy (1989)
M. Olivo, SGP (1988)
H. S. Pitkow (1988)
C. F. Rothe (1988)
M. Siegman, SGP (1988)
W. S. Spielman (1988)

**Finance**
F. J. Haddy, Chair (1989)
N. R. Alpert (1988)
J. D. Wood (1988)

**Financial Development**
J. B. West, Chair (1988)
F. M. Abboud (1989)
G. F. Cahill, Jr. (1989)
S. Chien (1989)
T. Cooper (1987)
R. W. Rennie (1987)
C. A. Sanders (1988)

**Honorary Membership**
R. W. Berliner, Chair (1987)
E. Knobil (1988)
E. H. Wood (1989)

**International Physiology**
A. P. Fishman, Chair (1987)
F. J. Haddy (1987)
F. G. Knox (1987)
H. E. Morgan (1987)
K. Schmidt-Nielsen (1987)
J. B. West (1987)

**Liaison with Industry**
N. B. Marshall, Chair (1988)
P. T. Beall (1987)
R. Beeuwkees (1988)
D. L. Costill (1989)
S. F. Flaim (1987)
A. M. Lefer (1988)
C. V. Gisolfi, ex officio (1988)
J. A. Spitzer, ex officio (1987)
R. J. Traystman, ex officio (1987)

**Long-Range Planning**
W. C. Randall, Chair (1987)
F. G. Knox (1987)
X. J. Musacchia (1987)
J. P. Granger (1988)
G. A. Hedge (1988)
S. G. Schultz (1989)
J. B. West (1989)

**Membership**
A. E. Taylor, Chair (1988)
N. M. Buckley (1987)
C. Levinson (1987)
S. Lahiri (1988)
L. C. Weaver (1988)
S. H. White (1989)

**Perkins Memorial Fellowship**
J. R. Pappenheimer, Chair (1989)
S. Chien (1989)
J. N. Diana (1988)
R. H. Kellogg (1989)

**Porter Physiology Development**
A. C. Barger, CoChair (1989)
E. L. Ison-Franklin, CoChair (1987)
D. L. Crandall (1989)
T. G. Coleman (1988)
P. J. Gunther-Smith (1989)
G. Kaley (1988)
J. W. Manning (1987)
E. L. Pautler (1987)

**Program Executive**
C. V. Gisolfi, Chair (1988)
P. D. Harris (1987)
S. K. Hong (1989)
L. G. Navar (1989)
M. L. Entman, ex officio (1988)
H. V. Sparks, Jr., ex officio (1987)

**Program Advisory**
(Section Appointments)
Cardiovascular—A. W. Cowley, Jr. (1987) and J. W. Downey, ex officio
Cell and General Physiology
P. J. DeWeer (1987)
Clinical Physiology
J. F. Biebuyck (1988)
Comparative Physiology
L. I. Crawshaw (1987)
Endocrinology and Metabolism
G. A. Hedge (1987)
Environmental, Thermal and Exercise Physiology—D. Robertshaw (1989)
Gastrointestinal Physiology
L. Lichtenberger (1987)
History of Physiology
N. C. Staub (1987)
Nervous System—J. Trubatch (1987)
Neural Control and Autonomic Regulation—M. I. Phillips (1987)
Renal Physiology—W. F. Boron (1987) and R. G. O'Neill (1989)
Respiratory Physiology
A. E. Taylor (1989)
Teaching of Physiology
J. Michael (1989)
Water and Electrolyte Homeostasis
E. H. Blaine (1988)
Epithelial Transport Group
R. A. Frizzell (1988)
MYOBIO Group—M. Siegman (1987)

**Public Affairs Executive**
R. L. Malvin, Chair (1989)
A. C. Barger, (1989)
K. D. Gardner (1987)
N. B. Marshall, ex officio (1988)
W. M. Samuels, ex officio

**Public Affairs Advisory**
Alabama—S. F. Gottlieb
Arkansas—L. K. Miller
Arizona—P. C. Johnson
Arkansas—G. S. Campbell
California—E. A. Rhode
Colorado—D. Robertshaw
Connecticut—R. W. Berliner
Delaware—F. E. South
Florida—M. E. Foreman
Georgia—D. H. Humphrey
Hawaii—M. D. Rayner
Idaho—T. H. McKean
Illinois—B. A. Curtis
Indiana—E. E. Selkurt
Iowa—R. E. Engen
Kansas—J. L. Voogt
Kentucky—H. R. Hirsch
Louisiana—T. H. Dietz
Maine—J. M. Norton
Maryland—T. R. Hendrix
Massachusetts—D. M. Philbin
Michigan—H. V. Sparks, Jr.
Minnesota—To be announced
Mississippi—M. Petrini
Missouri—D. M. Griggs, Jr.
Montana—J. A. McMillan
Nebraska—C. M. Moriarty
Nevada—R. Daugherty
New Hampshire—H. Valtin
New Jersey—G. F. Merrill
New Mexico—S. Solomon
New York—R. E. Dutton
North Carolina—M. L. Wolbarsht
North Dakota—T. K. Akers
Ohio—J. J. Curry
Oklahoma—K. J. Dormer
Oregon—A. J. Rampone
Pennsylvania—J. R. Neely
Rhode Island—H. F. Cserr
South Carolina—B. T. Cole
South Dakota—E. Schlenker and H. E. Grotjon
Tennessee—J. C. Ross
Texas—C. Desjardins
Utah—J. H. Petajan
Vermont—N. R. Alpert
Virginia—S. Price
Washington—H. D. Patton
West Virginia—G. A. Hedge
Wisconsin—J. A. Will
Wyoming—S. L. Lindstedt

**Publications**
P. J. Johnson, Chair (1988)
J. S. Cook (1989)
W. F. Ganong (1987)
L. R. Johnson (1987)
J. McE. Marshall (1988)

**Section Advisory**
M. Siegman, Chair (1987)
Cardiovascular Section
L. B. Rowell (1987)
Cell and General Physiology Section
L. Reuss (1989)
Comparative Physiology Section
R. B. Reeves (1987)
Endocrinology and Metabolism Section
L. S. Jefferson (1989)
Environmental, Thermal and Exercise Physiology Section—D. Robertshaw (1989)
Gastrointestinal Physiology Section
N. Weisbrodt (1986)
History of Physiology Section
N. C. Staub (1988)
Nervous System Section
J. Trubatch (1987)
Neural Control & Autonomic Regulation Section—V. S. Bishop (1986)
Renal Physiology Section
L. P. Sullivan (1987)
Respiratory Physiology Section
J. A. Nadel (1987)
Teaching of Physiology Section
H. Modell (1990)
Water and Electrolyte Homeostasis Section—A. W. Cowley, Jr. (1987)
Epithelial Transport Group
R. Frizzell (1988)
MYOBIO Group—M. Siegman (1987)

**Senior Physiologists**
A. B. Otis, Chair (1987)
E. F. Adolph (1988)
R. W. Berliner (1989)
R. O. Greep (1987)
R. E. Johnson (1989)
E. E. Selkurt (1987)
B. W. Zweifach (1987)

**Women in Physiology**
H. J. Cooke, Chair (1988)
C. Chew (1989)
B. C. Hansen (1987)
B. Horwitz (1989)
H. D. Van Liew (1987)

## Society Representatives to Other Organizations

**Amerian Association for Accreditation of Laboratory Animal Care**
L. Ramazzotto (1989)

**American Association for the Advancement of Science**
M. I. Phillips (1989)
L. C. Senay, Jr. (1989)

**American Institute of Biological Sciences**
M. Frank (Indefinite)

**Council of Academic Societies of the Association of American Medical Colleges**
G. A. Hedge (1987)
J. L. Kostyo (1989)

**Federation of American Societies for Experimental Biology**
*Board*
F. G. Knox (1988)
H. E. Morgan (1987)
H. V. Sparks, Jr. (1989)
*Executive Committee*
F. G. Knox (1988)
*Executive Officers Advisory Committee*
M. Frank (Indefinite)
*Education Committee*
J. A. Spitzer (1987)
*Federation Proceedings Editorial Board*
M. L. Entman (1988)
*Finance Committee*
H. E. Morgan (1988)
*Life Sciences Advisory Committee*
W. B. Seevers (1988)
*Meetings Committee*
C. V. Gisolfi (1987)
*Program Committee*
M. Frank (Indefinite),
*Public Affairs Committee*
K. D. Gardner (1988)
*Public Information Committee*
M. Cassidy (1988)
*Publications Committee*
L. R. Johnson (1988)
*Research Conference Advisory Committee*
C. V. Gisolfi (1988)
M. S. Smith (1987)
*3M Life Science Award Committee*
J. P. Filkins (1987)

**National Association for Biomedical Research**
M. Frank (Indefinite)

**US National Committee for IUPS**
A. P. Fishman (1989)
F. G. Knox (1988)
J. B. West (1987)
H. V. Sparks, Jr., ex officio
M. Frank, ex officio

**US National Committee on Biomechanics**
S. Chien (1987)

**MOVING?**

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# Membership Status

| | |
|---|---|
| Regular | 4,574 |
| Emeritus | 636 |
| Honorary | 14 |
| Corresponding | 143 |
| Associate | 761 |
| Student | 175 |
| Total | 6,303 |

## NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the Society at the Spring Meeting, 1986.

### Regular

**H. Richard Adams**
Univ. of Missouri

**Thomas K. Aldrich**
Montefiore Med. Ctr.

**Terence C. Amis**
Univ. of California, Davis

**Lawrence E. Armstrong**
US Army Research Inst. of Environ. Med.

**David B. Averill**
Cleveland Clinic Foundation

**Peggy L. Barrington**
Oklahoma Med. Research Foundation

**Gary L. Baumbach**
Univ. of Iowa Hospital

**Claude R. Benedict**
Univ. of Texas Medical Branch

**Bruce A. Biagi**
Ohio State Univ.

**Julien F. Biebuyck**
Pennsylvania State Univ.

**George E. Billman**
Ohio State Univ.

**Martha L. Blair**
Univ. of Rochester

**Babetta A. Brcuhaus**
North Carolina State Univ.

**Tommy A. Brock**
Brigham & Women's Hospital

**Thomas F. Burks**
Univ. of Arizona Hlth. Sci. Ctr.

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**William M. Chilian**
Univ. of Iowa

**Ira S. Cohen**
SUNY at Stony Brook

**Carol A. Colton**
National Institutes of Health

**Kirk P. Conrad**
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**Victor A. Convertino**
The Bionetics Corporation

**Edward F. Coyle**
Univ. of Texas

**Roy M. Culpepper**
Medical College of Virginia

**Michael J. Davis**
Texas A & M Univ.

**Primal De Lanerolle**
Univ. of Illinois

**Michael S. Dekin**
Univ. of Iowa

**Frederik J. Derksen**
Michigan State Univ.

**Anthony F. Dimarco**
Cleveland Metro. General Hospital

**Susanna J. Dodgson**
Univ. of Pennsylvania

**Sue K. Donaldson**
Univ. of Minnesota

**Krystyna Drewnowska**
Medical College of Virginia

**Frank W. Edens**
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**Robert L. Engler**
VA Medical Center, San Diego

**William L. Eschenbacher**
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**Peter A. Farrell**
Univ. of Wisconsin, Milwaukee

**William J. Federspiel**
The Biomechanics Institute

**Richard A. Fenton**
Univ. of Massachusetts

**Mario Feola**
Texas Tech Univ.

**Mark L. Fidelman**
Medical College of Virginia

**Ronald R. Fiscus**
Loyola Univ.

**J. Fernando Garcia-Diaz**
Boston Univ.

**Phyllis I. Gardner**
Stanford Univ.

**J. Jay Gargus**
Emory Univ.

**Bruce L. Gwertz**
Univ. of Chicago

**Daniel M. Gibbs**
Univ. of California, San Diego

**Christopher J. Gordon**
US Environmental Protection Agency

**Mark L. Graber**
VA Medical Center, Northport

**Felix E. Grissom**
Howard Univ.

**Sandra E. Guggino**
National Institute of Aging

**Jagdish Gulati**
Albert Einstein College of Med.

**Brian D. Guth**
Univ. of California, San Diego

**Patricia A. Gwirtz**
Texas Coll. of Osteopathic Medicine

**Calvin C. Hale**
Dalton Research Center

**Andrea Harabin**
Naval Medical Research Institute

**Dale A. Hartupee**
Univ. of Louisville

**William W. Hay, Jr.**
Univ. of Colorado

**Thomas A. Hazinski**
Vanderbilt Univ.

**William F. Holt**
Pfizer Central Research

**Christopher N. Honda**
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**Edward T. Howley**
Univ. of Tennessee

**Michael S. Hudecki**
SUNY at Buffalo

**Millie Hughes-Fulford**
NASA

**Adam N. Hurewitz**
SUNY at Stony Brook

**Thomas W. Hurley**
Univ. of Missouri

**Virginia H. Huxley**
Univ. of Missouri

**Rolf L. Ingermann**
Univ. of Idaho

**Thomas E. Jackson**
Univ. of Mississippi

**Roger D. Kamm**
Massachusetts Institute of Technology

**Harvey R. Kaslow**
Univ. of Southern California

**James C. Keith, Jr.**
Virginia Polytechnic Inst.

**Joseph W. Kemnitz**
Wisconsin Regional Primate Research Ctr.

**Ali A. Khraibi**
Bowman Gray School of Medicine

**Harold G. Klemcke**
US Dept. of Agriculture

**Douglas R. Knight**
Naval Submarine Medical Research Lab.

**John P. Koepke**
Univ. of Iowa

**Charles H. Lang**
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**Derek Leroith**
National Institutes of Health

**Warren E. Lockette**
Henry Ford Hospital

**Craig D. Logsdon**
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**Yvonne T. Maddox**
Georgetown Univ.

**Jacques Malo**
Hospital Sacre-Coeur

**Godfrey C.-W. Man**
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**Richard Moalli**
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**Ruth T. Moore**
Wayne State Univ.

**Lorin J. Mullins**
Univ. of Maryland, Baltimore

**Christopher Murlas**
Univ. of Cincinnati

**William R. Murphy**
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**Norbert R. Myslinski**
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**Judith A. Neubauer**
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**Edward J. Olender**
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**Anthony M. Paradiso**
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**Enrique Pastoriza**
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Univ. of Kuwait

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Xue-Han Ning
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Free Univ. of Berlin

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Wolf R. See
Albert Einstein Coll. of Med.

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Iwate Medical Univ.

Jose Vina
Univ. of Valencia

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Univ. of Berne

Amazia Zimber
Hebrew Univ. of Jerusalem

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Wyeth Laboratory

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Univ. of Nebraska

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Ohio State Univ.

Maret J. Panzenbeck
Univ. of Nebraska

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National Institutes of Health

Richard A. Peabody
National Institutes of Health

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Univ. of Virginia

Ruth E. Rollin
Univ. of North Carolina

Fred D. Romano
Univ. of Massachusetts

Mildred Audrey Rudd
Univ. of North Carolina

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VA Medical Center, East Orange, NJ

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Univ. of California, Davis

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Albany Med. College

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Kansas State Univ.

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Hartline Sci. Ctr.

Robert H. Thomsen
Georgia College

Mary L. Tod
Johns Hopkins Univ.

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Univ. of North Carolina

Elizabeth M. Wagner
Francis Scott Key Medical Ctr.

Stanley J. Whidden
JESMC Baromedical Research Inst.

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Univ. of California, San Diego

Lori L. Woods
Univ. of Mississippi

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Wright State Univ.

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Indiana Univ.

Elizabeth Crandall
Pennsylvania State Univ.

Gudrun Dieberg
Auburn Univ.

James P. Dixon
St. Louis Univ.

William H. Dubell, Jr.
Temple Univ.

Scott W. Duncan
Med. Coll. of Virginia

Julie Ann Dunn
Univ. of Tennessee

Kathleen A. Flatley
Loyola Univ., Stritch Sch. of Med.

Marc W. Gerdisch
Loyola Univ.

Jeffrey M. Gidday
Univ. of Virginia

Arrie Lynelle Golden
Univ. of Tennessee

Donald S. Houston
Mayo Clinic & Mayo Foundation

Sharon Inman
Univ. of Akron

## John F. Perkins, Jr. Memorial Award

The American Physiological Society invites applications for the John F. Perkins, Jr. Memorial Fellowships. The fund is designed to provide supplementary support to the familes of foreign physiologists who have arranged for fellowships or sabbatical leave to carry out scientific work in the United States. Applications by US physiologists who require supplementary assistance to work abroad will also be considered.

It is the interest of the Perkins Fund to develop the full potentialities for cultural benefit associated with scientific exchange. Preference will be given to physiologists working in the fields of respiratory physiology, neurophysiology, and temperature regulation.

Each application should be made by both the visiting scientist and his host. Ordinarily, the joint applicants will have made financial arrangements for the visiting scientist before applying to the Perkins Fund for family support. The application should contain an account of these arrangements with a description of the proposed scientific work and a brief account of how the visitor and his family intend to make use of the cultural benefits.

The amount available for each award will be in the range of $3,000–7,500, depending on the estimated needs of the family over and above the amount already available to the visiting scientist. Ordinarily, two to four awards will be available in any one year.

Application forms for host and visiting scientist may be obtained from Dr. Martin Frank, Executive Secretary, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814.

## Fifty-Year Members and Year of Election

Edward F. Adolph, 1921
Errett C. Albritton, 1933
Willard M. Allen, 1934
S. Howard Bartley, 1935
John W. Bean, 1932
Richard J. Bing, 1922
T. E. Boyd, 1925
Emil Bozler, 1932
Chandler McC. Brooks, 1933
Paul C. Bucy, 1933
Emmett B. Carmichael, 1931
K. K. Chen, 1929
Robert W. Clarke, 1936
Madeleine F. Crawford, 1933
Ray G. Daggs, 1935
Hallowell Davis, 1925
H. Hugh Dukes, 1934
Louis B. Flexner, 1933
Florent E. Franke, 1934
Maurice H. Friedman, 1929
Frederic A. Gibbs, 1935
Arthur S. Gilson, Jr., 1927
Harold D. Green, 1936
Chester W. Hampel, 1936
A. Baird Hastings, 1927
Joseph M. Hayman, Jr., 1928
John W. Heim, 1936
Frances A. Hellebrandt, 1933
Hebbel E. Hoff, 1933
Charles B. Huggins, 1932
Janes Sands Robb Johnson, 1925
Joseph L. Johnson, 1934
Frederic T. Jung, 1930
Nathaniel Kleitman, 1923
Eugene M. Landis, 1928
Arnold Lieberman, 1931
Ade T. Milhorat, 1934
Robert S. Morison, 1936
Hayden C. Nicholson, 1932
Herbert Pollack, 1933
C. Ladd Prosser, 1935
Paul Reznikoff, 1927
Oscar W. Richards, 1934
Curt P. Richter, 1924
John J. Sampson, 1932
Carl F. Schmidt, 1929
Francis O. Schmitt, 1930
James A. Shannon, 1933
Herbert Silvette, 1933
Paul W. Smith, 1933
Franklin F. Synder, 1936
Samuel Soskin, 1930
Isaac Starr, 1929
Eugene U. Still, 1928
Maurice L. Tainter, 1929
Sarah S. Tower, 1932
George E. Wakerlin, 1933
C. Beecher Weld, 1936
Robert A. Woodbury, 1936
Leland C. Wyman, 1927

**MEMBERSHIP** (*Continued from p. 72*)

**Noel L. Johnson**
Univ. of Virginia

**Michael J. Joyner**
Univ. of Arizona

**Gregory M. Karst**
Univ. of Arizona

**Jeffrey W. Kiel**
Univ. of Texas Hlth. Sci. Ctr.

**David S.-C. Lee**
Univ. of Manitoba

**Leslie Lescale-Matys**
Univ. of Southern California

**David W. Lipke**
Indiana Univ.

**John N. Lorenz**
Univ. of Kentucky

**Andreas S. Luebbe**
Univ. of Louisville

**David S. Miller**
California State Polytech. Univ.

**Bohdan M. Minczak**
Temple Univ.

**Susan M. Rausch**
Univ. of California, Los Angeles

**Gerald L. Sardella**
Dartmouth Med. Sch.

**Wendy E. Scales**
Univ. of Michigan

**Michael S. Shetzline**
Ohio State Univ.

**W. Fred Taylor**
Univ. of Texas Hlth. Sci. Ctr.

**Harry A. Tracy, Jr.**
Univ. of New Mexico

**Vicky L. Tucker**
Univ. of Missouri

**Michele G. Ulrich**
Univ. of South Alabama

**Michael Vassilyadi**
McGill Univ.

**Arthur W. Wallace**
Johns Hopkins Med. Sch.

**Margaret R. Warner**
Northwestern Univ.

**Meredith L. Warshaw**
Univ. of Illinois, Chicago

**Marsha A. Wills**
Univ. of California, Santa Barbara

**Karen M. Wilson**
Univ. of Florida

**Hal F. Yee, Jr.**
UCLA

**Mary Renee Zwallen**
Univ. of Akron

## Deaths Reported Since 1985 Fall Meeting

John P. Baker, Jr., Univ. of Texas Medical Branch, Galveston, TX (1983)
Marion I. Barnhart, Wayne State Univ. School of Medicine, Detroit, MI (12/23/85)
William A. Briscoe, New York, NY (12/21/85)
Berry Campbell, Monrovia, CA (11/21/85)
Marie C. D'Amour, Applegate, CA (10/84)
Dorothy T. Krieger, Mt. Sinai School of Medicine, New York, NY (4/02/85)
Harold A. Lyons, Sands Point, NY (8/26/84)
Hyman S. Mayerson, New Orleans, LA (10/85)
William A. Neely, Univ. of Mississippi, Jackson, MS (11/22/85)
Morton J. Oppenheimer, Norristown, PA (11/85)
Kenneth W. Perry, ICI Americas, Inc., (Death reported), Wilmington, DE (10/23/85)
David M. Rioch, Chevy Chase, MD (9/11/85)
Howard H. Rostorfer, Sevierville, TN (12/16/85)
Vladimir P. Skipski, Pelham, NY (10/01/84)
Helen R. Strausser, Rutgers Univ., Newark, NJ (1/17/86)
John M. Weller, Ann Arbor, MI (6/84)

## Founders Day!

Ohio Physiological Society

For APS, Founders Day is December 30, 1887, a day that will be celebrated at our Centennial Meeting in Washington, DC. However, for the Ohio Physiological Society (OPS), Founders Day is May 7, 1986. On that day, in Dayton, OH, Peter K. Lauf held the OPS' Founders Meeting in an auditorium at Wright State University School of Medicine. Much like the founders of APS, Peter Lauf thinks that the founding of OPS will help "to enhance and advance the field of physiology ... and unite the physiologists for this purpose."

The founding of the Ohio Physiological Society followed the Fourth Annual Symposium of the Biomedical Sciences Ph.D. Program. The symposium, entitled "Properties and Regulation of Water and Ion Transport in Health and Disease," featured nationally and internationally recognized investigators discussing exciting aspects of cellular and molecular physiology. The content of the symposium reflected Dr. Lauf's view of the importance of cellular and molecular approaches in physiology.

Prior to the meeting and symposia, invitations had been sent to physiologists throughout Ohio. The result was a founders meeting attended by scientists from a number of Ohio departments of physiology. The attendees passed bylaws and elected officers for the 1st year. The officers of the Ohio Physiological Society are President, Peter K. Lauf: Wright State University; President-Elect, Bruce Biaggi, Ohio State University; and Secretary-Treasurer, Noel Nussbaum, Wright State University. The next order of business for the new society is their first scientific meeting, scheduled for November 1986.

Physiologists desiring more information about the Ohio Physiological Society should contact Dr. Peter K. Lauf, Chair, Department of Physiology and Biophysics, Wright State University School of Medicine, Dayton, OH 45435.

NEWS FROM SENIOR PHYSIOLOGISTS

(*Continued from p. 68*)

sional lecture, I'm having a marvelous time at work which is my form of play." He finds analyzing data to be much more fun than trying to answer the philosophical questions that underlie the committee's inquiry about how he is faring.

**Richard O. Recknagel** is officially retiring this year from Case Western Reserve University. If all goes well, his NIH grant will be renewed for another 5 years and he will continue research with his colleague, Dr. E. A. Glende, Jr. He writes, "I have the following words of wisdom which I pass on to younger investigators: BELIEVE NOBODY."

**James T. Bradbury**, retired since 1974 from the University of Montana, thanks the committee for its greetings on the occasion of his 80th birthday. He reports that in March he was presented the President's Distinguished Scientist Award of the Society for Gynecologic Investigations of which he is a past-president. He recommends that academicians retire in the vicinity of a university where attendance at seminars and a library provide a nice transition to full-time retirement.

**John V. Taggart** writes that his early years were spent in departments of medicine, and then from 1962 to 1982 he was thoroughly immersed in the activities of the Department of Physiology at Columbia. Since retirement 4 years ago, his interests have reverted to internal medicine, doing postgraduate courses, and participating in clinical conferences in an excellent suburban community hospital. He has found a complete change of pace every 20 years to be refreshing and stimulating.

**Morris ("Rocky") Rockstein** has passed his 70th birthday but is pumping iron three times a week, playing (at) singles tennis, and swimming laps. He is also busy wearing two hats as a consultant for AIBS for lecture workshops at minority student universities and as editor of the two major monographic series of the Entomological Society of America. He notes that as a physiologist he "discovered" insects as a prime group of laboratory experimental animals. He gives frequent lectures on gerontology to professional and university audiences as well as to the public at large.

# PUBLIC AFFAIRS

## Bill Would Bar NIH Funds for Pound Animals

Rep. Robert J. Mrazek (D-NY) has introduced what he calls the "Pet Protection Act of 1986" (HR 4871), which would prohibit the use of NIH grant funds for obtaining unclaimed animals from pounds for the purpose of research.

The bill applies to any animal acquired "directly or indirectly from any animal shelter for any research purpose." An animal shelter is defined in the bill as any organization or governmental agency that cares for lost, stray, unwanted, abandoned, or homeless animals or is given custody animals seized under state or local laws.

The bill provides a penalty for violation of "immediate termination of funds for the project or research protocol."

Mrazek claims in a letter to colleagues that shelter animals are not suitable for use in research because nothing is known about their genetic, environmental, or medical backgrounds and that research involving such animals is "scientifically questionable" and that it is "widely recognized that such data obtained through research on shelter animals may not be scientifically valid."

He also states that the claim that shelter animals are less expensive than purpose-bred animals is a false economy because "shelter animals must undergo expensive conditioning" and "are more likely to become sick or die prematurely, and more (shelter animals) are required to complete identical research."

William M. Samuels, CAE

> Physiology is the queen of the biological sciences, a very fertile queen indeed for during the last century it gave rise to many daughters. These daughter disciplines are today recognized by names such as Physiological Chemistry or Biochemistry, Pharmacology, Biophysics, Bio-engineering. If one considers Anatomy to be a science of three dimensions, Physiology adds a fourth dimension, namely, time.
>
> Hermann Rahn

## To the Editor

I am what might be called a "backwater" physiologist. This is a physiologist who teaches for a living without the time or facilities to develop a fully active research program. While I spend less time doing research, I may spend more time thinking (and maybe even fantasizing) about potential projects. I read your editorial in *The Physiologist* [29(1): 1, 1986] and was concerned about the lack of understanding of the forces influencing the direction of physiological research. You see, when you discuss the directions of physiology, you are really discussing the management of science rather than science itself. If the American Physiological Society wants to understand the future direction of research, the leadership will need to identify the factors that determine what research is done. The real key lies in the basic difference between science and its management. In science, for most purposes, truth is reality. With science, if only one of 10 men in a room claims that the sky is blue (and the sky is blue), then the 9 others are incorrect even though they are a majority. In management, as in many human endeavors, perception tends to be reality. The majority are always correct, even when they are wrong. Let me try to discuss some of the forces that determine what research is done.

### Fads and Fancies

If one were to look at the directions of various departments of physiology, one would see various trends in research. For example, in the 40's and 50's, the emphasis was on gastrointestinal research. However, by the 60's there was a shift to cardiovascular physiology. In the 80's concern has shifted to the molecular biological aspects of physiology. Can we say that we have solved all the major problems in the areas that are no longer in fashion?

### Financial Aspects

To understand what the chairmen of the departments of physiology are trying to tell you when you were permitted to sit in on their meeting, you must also understand the forces that are operating on their management decisions. These management decisions really provide the direction for physiology in the coming years. The chairmen are primarily responsible for the financial stability of their various departments. Thus, the decisions on whom to hire are based on *1*) the financial support the individual can obtain and *2*) the ability to provide prestige to the institution. You will notice that I did not include teaching ability in this list (if they can afford to hire a molecular biologist to be retrained to teach physiology, teaching must not be that important). If the institution is large enough, others can be conscripted into teaching the courses. It is the first consideration to which I direct your attention. The larger the budget the investigator can substantiate, the greater the prize to the department, since it means the overhead as a percentage of the budget will result in more tangible dollars. We can now understand that the more exotic and the expensive the equipment, the more money that can be obtained for the running of the department. The second consideration, the prestige factor, ensures the financial support of less well-known members of the faculty.

### Technology

The various chairmen of departments of physiology in ***medical schools*** have indicated the need to remain at "the cutting edge of physiology." Can anyone tell me what "the cutting edge of physiology" really is? In reality, it is not the cutting edge of physiology but rather the cutting edge of technology. Several years ago someone suggested that technology may actually drive science rather than the reverse. It is a concept with which I completely agree. Research that is supported by grants is closer to "the cutting edge of technology" than nonsupported research. The general principle is the greater the technology, the more impressive the project.

I guess you are wondering why I wrote this letter. What I have given you is nothing more than standard management theory. What concerns me in the long run is that these people think that they are making good management decisions on the direction of physiological research within their respective departments. What is really happening is that they are being driven on by technological advances without their recognizing it. These people think that planning is taking place while to a large extent the direction is by whim. Today we are enamored of molecular biology. Where will we be in the future?

In a larger sense, if we examine the entire process on where physiology is heading over the next few years, we can see that two types of decisions should be made. The first type, or short-term decisions (decisions affecting the direction of research for one year), is currently being made in peer-review committees. I do not object to this method except that unlike industrial situations, where managers are fully aware of the implications of their decisions, average members of peer-review committees are not aware of how much their decisions affect the future direction of physiological research. The second type of decision concerning the long-term direction of physiological research is just not being made. Perhaps this is one area in which APS should take a leadership position.

Zalmon Pober
Associate Professor of Physiology and Pharmacology
Massachusetts College of Pharmacy and Allied Health Sciences

### Future Meetings

| | |
|---|---|
| 1986 | |
| APS Fall Meeting | October 5–9, New Orleans |
| 1987 | |
| * FASEB Annual Meeting | March 29–April 3, Washington, DC |
| APS Fall Meeting | October 11–16, San Diego |
| 1988 | |
| FASEB Annual Meeting | May 1–6, Las Vegas |
| Joint APS/ASPET Fall Meeting | October 9–14, Montreal |
| 1989 | |
| FASEB Annual Meeting | March 19–24, New Orleans, LA |
| APS Fall Meeting | October 15–19, Rochester, NY |

* APS Centennial Celebration

# ANNOUNCEMENTS

## Rijlant Triennial Prize for Cardiac Electrophysiology

The Professor Pierre Rijlant Triennial Prize for Cardiac Electrophysiology (1985–1987) will be conferred to the author or the authors, members of a team, for a work bringing about a major contribution in the following fields: hybrid computer in electrocardiography; application of computer to electrocardiography; electro- and vectography and analogic simulation; or any field of cardiac electrophysiology. The work must be written in the French, Dutch, English, or German language. There will be no discrimination according to nationality of the author or authors. Works already rewarded with an university prize or a national or international prize of an amount at least equivalent, as well as those presented by an author who would have received such a prize during the 3 preceding years, will not be taken into consideration. Amount of the prize: 500,000 Belgian francs (approximately 10,000 US dollars, at the present exchange rate). Deadline date for submission of papers: December 31, 1987.

## ONR Young Investigators Program, FY87

The Office of Naval Research (ONR) is announcing another cycle of its program to identify and support young scientists. This program is open to US citizens holding tenure-track positions at US universities and colleges who received their doctoral degrees on or after January 1, 1982. In 1985 awards of no less than $50,000 per year for 3 years, with the possibility of greater support through matching funds, were made, based on the research proposals and supporting material received. Proposals falling within the broad scope of naval research interests as described in the Office of Naval Research book *Guide to Programs* (available from the address noted below) will be considered. Applications must be submitted by early December 1986, and awards will be made in the spring of 1987. Further information can be obtained from Dr. R. Newburgh, Head, Biological Sciences Division, Office of Naval Research, 800 N. Quincy St., Arlington, VA 2217. Phone: (202)696-4986.

## Volvo Awards for Low-Back-Pain Research

To encourage research in low back pain, the Volvo Company of Göteborg, Sweden, this year has sponsored three prizes, now increased to US $7,000 each. Awards will be made competitively on the basis of scientific merit in the following three areas: clinical studies, bioengineering studies, studies in other basic science areas.

Papers submitted for the contest must contain original material, not previously published or submitted for publication. A multiple authorship is acceptable. The manuscripts should be in the form of a complete report, including original illustrations, not exceeding 30 typewritten pages, double-spaced, and in a form suitable for submission to a scientific journal. Five copies of each paper submitted in full should reach the address given below not later than December 15, 1986.

One of the authors should be prepared, at his own expense, to come to Rome, Italy, at the time of the meeting of the International Society for the Study of the Lumbar Spine, May 24–28, 1987, to present the paper and to receive the award.

A board of referees will be chaired by the undersigned and will contain members from the fields of clinical medicine, bioengineering, and biochemistry. Please direct all correspondence to Professor Alf L. Nachemson, Department of Orthopaedic Surgery, Sahlgren Hospital, S-413 45 Göteborg, Sweden.

## Pfizer Hospital Products Group announces grant

Pfizer Hospital Products Group has announced a $50,000.00 research grant for an original invention in the medical device area. Those applying for the grant should be professionals active in one of the branches in the health-care field. The submitted proposal will be evaluated by an outside panel of experts. Influencing the decision will be the scientific merit of the invention and its benefit to the patient. Consideration will be given to the practical application of the invention and its possible impact on the quality of health care. Applications will be held in confidence and must be received no later than December 15, 1986. Materials can be ordered by writing to George Flouty, M.D., Pfizer Hospital Products Group, Research Grant for Innovation, Pfizer, Inc., 235 East 42nd St., New York, NY 10017.

## Biomedical Simulations Resource

A Biomedical Simulations Resource (BMSR) has been established at the University of Southern California through a 5-year grant from the Division of Research Resources of the National Institutes of Health.

The purpose of the Resource is to advance the state-of-the-art in modeling and simulation of biomedical systems through core research projects and facilitate the dissemination of this knowledge throughout the biomedical community. The latter will be accomplished through collaborative research projects, distribution of applications software, advanced short courses, annual workshops, and BMSR publications including a quarterly newsletter, technical reports, and annual workshop transactions.

The emphasis of the core research projects is on modeling methodologies regarding nonlinear, nonstationary, and sparse-data systems. Applications cover a wide range of biomedical domains, including respiratory physiology, neurophysiology, and pharmacokinetics. These modeling methodologies may also find fruitful applications to the studies of nonlinear and/or nonstationary engineering systems.

BMSR invites investigators interested in these research areas to join their mailing list by writing to Prof. Vasilis Z. Marmarelis, Director, Biomedical Simulations Resource, School of Engineering, University of Southern California, Los Angeles, CA 90089-1451, or call (213)743-3648, indicating the area(s) of particular interest.

## National Resource for Computers in Life Science Education Established

APS members interested in using computers in their teaching efforts will be interested to learn of the establishment of the National Resource for Computers in Life Science Education (NRCLSE). NRCLSE is a nonprofit organization aimed at cultivating collaborative efforts among faculty with expertise in using computers in life science education. The concept grew, in part, from the APS education committee-sponsored workshops and symposia in this area and from the committee's attempt to identify colleagues active in this area.

The overall goals of the resource are to *1)* educate faculty in effective uses of computers in the curriculum; *2)* promote development of a critical mass of high-quality, versatile software; *3)* initiate research aimed at evaluating new applications of the computer to life science education; and *4)* serve in a consultant capacity for life science faculty currently active in this area.

The initial projects of the resource include publishing a monthly newsletter, *Computers in Life Science Education*, available on a subscription basis for $30 per year; identifying the critical mass of life science educators with expertise in this area; establishing a peer-critique mechanism for software, and disseminating a limited amount of software (currently in respiratory physiology).

For further information, contact Dr. Harold Modell, Director, NRCLSE, Mail Stop RC-70, University of Washington, Seattle, WA 98195. Phone: (206)548-6244.

## La Pression Barometrique

The translation of Paul Bert's *La Pression Barometrique*, which was done by Mary Alice and Fred Hitchcock, is available through the Undersea Medical Society.

In 1978 the Society realized that this important work was out of print and decided to publish the English edition in hardcover. It was very popular, and when this supply became exhausted we decided to reprint (in 1985). These books are available from our Society at 9650 Rockville Pike, Bethesda, MD 20814.

## LSRO Reports Available

A report by the FASEB Life Sciences Research Office entitled *Assessment of the Vitamin A Nutritional Status of the U.S. Population Based on Data Collected in the Health and Nutrition Examination Surveys* is available. The report, sponsored by the Center for Food Safety and Applied Nutrition, FDA, provides a description of the methodologies used to determine serum vitamin A levels for a representative sample of the US population in NHANES I, for a representative sample of children in NHANES II and for a sample of Mexican-Americans in the Southwest portion of HHANES. The final report of the LSRO ad hoc Expert Panel on NHANES III Recommendations entitled *Suggested Measures of Nutritional Status and Health Conditions for the Third National Health and Nutrition Examination Survey* is also available. Copies of these reports are $14.00 for the vitamin A report and $24.00 for the NHANES III report. Orders should be sent to FASEB Special Publications Office, 9650 Rockville Pike, Bethesda, MD 20814.

## Conference on Welfare of Laboratory Animals

The Scientists Center for Animal Welfare announces a conference, "The Welfare of Laboratory Animals: Current Issues," to be held in cooperation with the University of Texas System Cancer Center. The conference will be held on October 16–17, 1986, in Houston, TX.

For more information contact Dr. F. Barbara Orlans, Director, Scientists Center for Animal Welfare, 4805 St. Elmo Ave., Bethesda, MD 20814. Phone: (301)654-6390. Also, Dr. Kenneth Gray, University of Texas System Cancer Center, Veterinary Medicine and Surgery, 6723 Bertner, Box 63, Houston, TX 77030. Phone: (713)792-2780.

## Scientific Meetings and Congresses

X World Congress on Cardiology, Washington, DC, September 14–19, 1986.

IUPS Commission on Gravitational Physiology 8th Annual Meeting, Tokyo, Japan, November 4–8, 1986.

Society of Neuroscience Annual Meeting, Washington, DC, November 9–14, 1986.

American Society for Cell Biology, Washington, DC, December 7–11, 1986.

American Society of Zoologists Meeting, Nashville, TN, December 27–30, 1986.

1986 21st Annual Scientific Meeting of the European Society for Clinical Investigation, Elsinore, Denmark, March 21–24, 1987.

2nd World Congress of Neuroscience, Budapest, Hungary, August 16–21, 1987.

Xth International Congress of Pharmacology, Sydney, Australia, August 23–28, 1987.

# BOOKS RECEIVED

*How it Was. Anabolic Action of Steroids and Remembrances.* C. D. Kochakian. $10.95.

*Anatomy and Physiology Laboratory Manual.* Second Edition. G. J. Tortora and N. P. Anagnostakos. Minneapolis: Burgess, 1986, 468 pp., illus., index, $15.95.

*Cardiovascular Physiology. Second Edition.* D. E. Mohrman and L. J. Heller. New York: McGraw-Hill, 1986, 212 pp., illus., index, $17.95.

*Circulatory Physiology—The Essentials. Second Edition.* J. J. Smith and J. P. Kampine. Baltimore, MD: Williams & Wilkins, 1984, 332 pp., illus., index, $15.20.

*Dictionary of Immunology. Third Edition.* W. J. Herbert, P. C. Wilkinson, and D. I. Scott (Editors). Oxford: Blackwell, 1985, 237 pp., illus.

*Experiments in Physiology. Fifth Edition.* G. D. Tharp. Minneapolis, MN: Burgess, 1986, 262 pp., illus., index, $13.60.

*Hormones, Receptors and Cellular Interactions in Plants.* C. M. Chadwick and D. R. Garrod (Editors). New York: Cambridge Univ. Press, 1986, 375 pp., illus., index, $69.50.

*Instrumentation for Environmental Physiology.* B. Marshall and F. I. Woodward (Editors). New York: Cambridge Univ. Press, 1986, 241 pp., illus., index, $34.50.

*Laboratory Outlines in Biology—IV.* P. Abramoff and R. G. Thomson. New York: Freeman, 1986, 529 pp., illus., $17.95.

*Neuromethods 1. General Neurochemical Techniques.* A. A. Boulton and G. B. Baker (Editors). Clifton, NJ: Humana, 1985, 576 pp., illus., index, $64.50.

*Principles of Human Physiology. Second Edition.* G. J. Tortora and R. L. Evans. New York: Harper & Row, 1986, 761 pp., illus., index.

*Pulmonary Physiology. Second Edition.* M. G. Levitzky. New York: McGraw-Hill, 1986, 276 pp., illus., index, $17.95.

*The Roots of Molecular Medicine. A Tribute to Linus Pauling.* R. P. Huemer (Editor). New York: Freeman, 1986, 290 pp., illus., index, $21.95.

*The Vital Force: A Study of Bioenergetics.* F. M. Harold. New York: Freeman, 1986, 577 pp., illus., index, $37.95.

# BOOK REVIEW

## *DESIGN OF SMOOTH MUSCLE.*
## P. K. Rangachari and A. K. Grover (Editors)
Hamilton, Ontario: Image Publishing, 1985, 120 pp, illus, $29.95 (Canada)

The *Design of Smooth Muscle* is a collection of short essays gathered together as a Festschrift to honor Dr. Edwin E. Daniel on the occasion of his 60th birthday. The career of this internationally recognized Canadian physiologist/pharmacologist has spanned more than 30 years and has dealt with an impressive array of research problems in smooth muscle biology. The eclectic nature of Dr. Daniel's research interests is well exemplified by the topics covered in this volume.

Each essay/chapter was contributed by an individual who has worked closely with Dr. Daniel, as a graduate student or collaborator, and who is now well respected in their own field of smooth muscle research. The intimate, personal perspective of these essays and the accompanying often humorous tributes to Dr. Daniel from scientists from around the world make interesting reading and give us a glimpse of the scientific contributions and the nature of an individual who has very few peers in smooth muscle research.

Each chapter deals with a different aspect of his work, and a quick perusal of the table of contents shows that almost every facet of smooth muscle research is covered. In general, each essay gives a historical perspective of Dr. Daniel's contribution and provides a current review of the field. Included are chapters on smooth muscle structure, cell-to-cell communication, electrophysiology, excitation-contraction coupling, gastrointestinal motility, and its pharmacological control, membrane biochemistry, sodium pump activity, and cell membrane receptors. The final two essays deal with Dr. Daniel's contributions to the study of smooth muscle pathophysiology in asthma and hypertension and demonstrate the multidisciplinary approach to research that he has utilized so effectively.

Although informative, the chapters do vary considerably in scientific content. For example, some essays are detailed reviews of the field and Dr. Daniel's personal contributions, while others are rather more anecdotal. As noted by the editors in the preface, this variability can be attributed to the extreme range of flexibility given to the contributors.

The *Design of Smooth Muscle* is not a comprehensive text on smooth muscle. It was not intended to be so. Rather it is an informative and frequently spicy personal look at the extent of Ed Daniel's impact on the field from those who have been associated with him.


### 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 December 15 for the February 1986 issue). Mail copy to APS, 9650 Rockville, Pike, Bethesda, MD 20814.

## PEOPLE AND PLACES . . .

**Richard K. Orkand**, Ph.D., of the University of Pennsylvania has been appointed Director of the Institute of Neurobiology at the Medical Sciences campus of the University of Puerto Rico. Dr. Orkand has been a member of APS since 1968 and formerly chaired the Section on the Nervous System.

APS member, **Arthur E. Baue**, M.D., Professor of Surgery and Associate Dean for Clinical Affairs in the School of Medicine at St. Louis University, has been appointed Vice President for the Medical Center.

**Albert L. Waldo**, M.D., has been named The Walter H. Pritchard Professor of Cardiology and Professor of Medicine at Case Western Reserve University School of Medicine. Dr. Waldo, formerly at the University of Alabama at Birmingham, School of Medicine, as Professor of Medicine and Director of the Specialized Center of Research in Ischemic Heart Disease, has been a member of the Society since 1973.

APS member, **Ralph L. Brinster**, V.M.D., Ph.D., Robert King Mellon Professor of Reproductive Physiology at the University of Pennsylvania, was 1 of 30 new members elected to the Institute of Medicine.

**William H. Sweet**, M.D., D.Sc., Senior Neurosurgeon of the Massachusetts General Hospital, was one of five persons elected to senior membership in the Institute of Medicine. Dr. Sweet has been a member of the Society since 1962.

## 1986 Election to National Academy of Sciences

**Ernst Knobil**, Ph.D., The Wayne Hightower Professor of Physiology, University of Texas Health Science Center at Houston, elected to the National Academy of Sciences for contributions to the field of pituitary physiology, was the first to show that only growth hormone extracted from primate pituitary glands was effective in primates, including the human. This discovery led to the development of radioimmunoassays for human growth hormone and permitted a host of investigations dealing with control of growth hormone secretion. Most importantly, however, evolved a rational model of the neurooendocrine control of the menstrual cycle that describes the ovarian hormones and the pituitary gland in the control of gonadotropin secretion and of ovarian function. Dr. Knobil, whose Society membership dates back to 1955, was elected President in 1978. He served on APS committees, the editorial boards of several Society journals, and was Editor of *American Journal of Physiology: Endocrinology and Metabolism*.

**T. P. Feng**, Director of the Institute of Physiology and member of the Chinese Academy of Sciences, has been elected to the National Academy of Sciences for his pioneering work on neuromuscular transmission. Dr. Feng's scientific achievements have received international recognition. His current research activities are chiefly concerned with trophic relations between nerve and muscle. While President of the Chinese Physiological Society, Dr. Feng was elected to Honorary membership in APS.

APS member **Robert Plonsey**, Ph.D., Professor of Biomedical Engineering and Physiology, Duke University, was elected to the National Academy of Engineering for the application of electromagnetic theory to biology and for distinguished leadership in the emerging field of biomedical engineering.

**Roger H. Unger**, M.D., Professor, University of Texas Southwestern Medical School at Dallas and Senior Medical Investigator, Dallas Veterans Administration, was elected to the National Academy of Sciences for establishing that glucagon is the major counterregulating hormone that, together with insulin, controls the balance of glucose production and glucose utilization. Dr. Unger, who has been a member of the Society since 1976, has been the recipient of many awards.

**Emilio Bizzi**, M.D., APS member since 1971 and a former editorial board member of the *Journal of Neurophysiology*, has been elected to the National Academy of Sciences for his studies on the coordination of eye-head movements. He now serves as Director of Whitaker College of Health Sciences, Technology and Management of Massachusetts Institute of Technology and has been the Eugene McDermott Professor in the Brain Sciences and Human Behavior, Department of Psychology at MIT.

**Rodolfo R. Llinas**, Professor and Chairman, Department of Physiology and Biophysics, New York University Medical Center, was elected to the National Academy of Sciences for structural and functional studies of neuronal systems and for his studies on transmission in vertebrate and invertebrate forms. A member since 1968, Dr. Llinas presented the APS Bowditch Lecture in 1973.

## Guggenheim Fellowships

The John Simon Guggenheim Memorial Foundation awards fellowships on the basis of unusually distinguished achievement in the past and exceptional promise for future accomplishment. Three APS recipients were **John G. Forte**, Professor of Physiology, University of California at Berkeley, for the cell biology of gastric acid secretion: **Alan D. Grinnell**, Professor of Physiology and Director of the Jerry Lewis Neuromuscular Research Center, University of California at Los Angeles, for nerve guidance and mechanisms of specificity in regeneration: and **Robert W. Schrier**, Professor of Medicine, University of Colorado, for studies in the molecular biology of the kidney.

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**USA-USSR EXCHANGE**
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meetings. This is only the first step in developing a closer and consistent relationship. It would be most desirable if APS would formulate an agreement to be signed by a delegation of both societies next year at the APS Centennial meeting in Washington, DC, or at the Soviet All-Union Congress in September.

Professor Ivantisky presented Dr. Howard Morgan with a medallion dedicating the 25th anniversary of the first spaceflight of the Soviet Union. In thanking him, Dr. Morgan said it would be placed in the Society's archives along with President Gazenko's letter so that scientists in the future will know of the contact desired by the two countries.

The opportunity for scientific exchange between the two countries is dependent on the signing of an agreement between APS and the All-Union Physiological Society. To that end, Dr. John West has been asked to coordinate efforts to develop an agreement and identify potential funding sources. It is hoped that a contract of mutual exchange between the two societies can be prepared by next year for signing, when Professor Gazenko comes to this country as a centennial guest.

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.

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**NSF**

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for receipt of the reviews and then call the program officer to discuss the proposal and the specifics of the review process. Often, program officers are able to relate nuances of the panel discussion that may not be evident from the panel summary. The program officer can also suggest to the PI which are the major points of concern about the proposal and how the PI might best respond to reviewer and panelist criticisms. PIs should not always expect to be able to resubmit for the target date immediately following the panel.

Many program officers in the biological sciences at NSF are "rotators" on leave from their universities. This means that after a year or two the program officer will be replaced by someone with perhaps a somewhat different point of view. Given the turnover and rotation of panelists, and the rotator system for most program officers, proposals that do not do well at one panel in one year may do better at another panel in another year, especially if the research has progressed and if the criticisms generated by the previous review have been constructively addressed in the resubmission.

Finally, the NSF has an appeals procedure for cases in which a PI feels that a serious error has been made in the review process. This reconsideration process concerns itself primarily with questions of procedure and fairness rather than providing a forum for scientific rebuttal. If it can be convincingly demonstrated that a proposal did not receive a fair scientific review, then the subsequent decision making can be called into question. The appeals process generally takes longer than resubmission and subsequent evaluation. Further information on the appeals procedure can be obtained from program officers or division directors.

The author thanks Dr. Maryanna Henkart, Director of the Cellular Physiology Program, for her helpful suggestions regarding this article.

# Know Your Sustaining Associates

**American College of Surgeons**

The American College of Surgeons is an association of surgeons organized for the primary purpose of improving the quality of care for the surgical patient by elevating the standards of surgical education and practice. In the pursuit of its goals for seven decades, it has profoundly influenced the course of scientific surgery in America.

The College has been a pioneer in establishing a nationwide program for hospital accreditation, in developing standards for the training of surgical residents, in setting guidelines for a high level of preoperative and postoperative care, and in organizing the resources of surgery in a major effort to improve the care of the critically injured accident victim and the patient with cancer.

Moreover, since its founding in 1913 the college has continuously and publicly denounced fee splitting, unjustified operations, itinerant surgery, and other practices detrimental to the welfare of patients and the public and has made adherence to its principles of surgical ethics a condition for obtaining and maintaining Fellowship.

**The 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.

**Dagan Corporation**

Dagan Corporation manufactures 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.

**Medtronic**

Medtronic, for a quarter century the world's leading implantable medical device company, today serves a broad cardiovascular marketplace. Growing capabilities in screening, diagnosis, and follow-up care now complement established therapeutics businesses such as heart pacemakers and valves. Also, for over a decade Medtronic has applied expertise in the electrical functions of the body to neurological stimulation products.

**Merrell Dow Research Institute**

Merrell Dow Research Institute, with centers in four countries and headquarters in Cincinnati, OH, is an interdisciplinary institution engaged in both basic and applied biomedical research. The institute identifies new targets and molecules that may be suitable for pharmacological intervention with an ultimate goal of developing new therapeutic agents.

**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.

**Stuart Pharmaceuticals**

Stuart Pharmaceuticals, division of ICI Americas, Inc., is one of the youngest research-based companies, founded in Pasadena, CA, in 1941.

Now headquartered in Wilmington, Delaware, Stuart is linked to the worldwide pharmaceutical research efforts of Imperial Chemical Industries, PLC, of London, with which it merged in 1972. These efforts have produced some of today's most important therapeutic agents such as the principal $\beta$-blocker for cardiovascular disease, the most widely prescribed single agent for breast cancer, and the leading antiseptic used in hospitals.

Current research promises to yield innovative products for infectious disease, anesthesia, heart disease, cancer, and diabetes.

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AMERICAN PHYSIOLOGICAL SOCIETY CENTENNIAL 1887-1987

# APS Sustaining Associate Members

The Society gratefully acknowledges the contributions received from Sustaining Associate Members in support of the Society's goals and objectives.

Abbott Laboratories
American College of Surgeons
American Critical Care
American Medical Association
Burroughs Wellcome Company
Ciba-Geigy Corporation
Coulbourn Instruments, Inc.
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Hoechst-Roussel Pharmaceuticals, Inc.
* Hoffman-La Roche, Inc.
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Lederle Laboratories
Lilly Research Laboratories
Marion Laboratories, Inc.
McNeil Laboratories
Merrell Dow Industries
* Merck Institute for Therapeutic Research
Medtronics, Inc.
Miles Institute for Preclinical Pharmacology
Pfizer, Inc.
Revlon Health Care Group
Pillsbury Corporation
A. H. Robins Company
Sandoz, Inc.
* Schering Corporation
G. D. Searle and Company
* Squibb Corporation
Stuart Pharmaceuticals
* The Upjohn Company
Waverly Press, Inc.
Wyeth Laboratories

* Second Century Corporate Founders

KNOW YOUR SUSTAINING ASSOCIATES
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**The Upjohn Company**

The Upjohn Company, a multinational corporation headquartered in Kalamazoo, MI, is celebrating 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, Inc.**

Waverly Press, Inc., are printers of magazines and journals for the association marketplace.

Committed to servicing their customers through sharing knowledge, providing the best in modern technology, and establishing mutual respect, they offer full-range publishing services including design, editorial, composition, printing, binding, mailing, 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 traditional at Waverly—one that continues. They believe in quality product and service through quality people.

## Second-Century Corporate Founders

As it enters its second century, the American Physiological Society is in the process of raising an endowment fund for scientific program development designed to foster vigorous and varied interactions between research scientists in the industrial sphere and those in academic institutions. Since 1887, when the Society was founded, APS has been devoted to fostering basic and applied scientific research, to education, and to the dissemination of scientific information. For APS to continue these activities into its second century, Norman Marshall, Chairman of the Liaison with Industry Committee, developed the concept of the endowment fund. After extensive discussion, the Society recruited a steering committee consisting of Theodore Cooper, Philip Felig, Robert Furman, Charles Sanders, Howard Morgan, Norman Marshall, and Martin Frank. The steering committee's charge has been to raise the first $250,000 of a projected $1,000,000 endowment fund.

The endowment fund provides the mechanism for the equitable distribution of resources to symposia organizers. Currently, the Society is unable to allocate sufficient resources to meet the needs of the program organizers seeking to attract prominent and key scientists as participants in their symposia. Thanks to the creativity of our symposia organizers and the generosity of corporations, the Society has been able to develop and program many outstanding symposia. However, repeated requests to corporations for contributions is frustrating to all parties. Thus, the purpose of the APS Program Endowment Fund is to raise sufficient resources from corporate and industrial sources, with matching funds from APS, to stabilize the Society's program activities and limit the need for numerous yearly requests to the same corporations to fund multiple symposia.

To convince corporations that their contribution to the endowment fund would eliminate multiple requests for symposia support, the Society has guaranteed companies making a significant contribution that no further requests would be authorized by APS. This has been accomplished by requesting that all symposia organizers work directly with the Executive Secretary-Treasurer to coordinate fund-raising activities.

The Society is pleased to announce that the concept of an endowment fund has been favorably received by a number of corporations. Corporations making significant contributions to the endowment fund will be identified as Second Century Corporate Founders in the box listing APS Sustaining Associates and duly recognized at the Centennial Meeting. To date, the Society is pleased to thank Hoffman-La Roche, Inc., Merck and Co., Inc., Schering Corporation, Squibb Corporation, and Upjohn Company for their contributions to the Second-Century Corporate Founders Program Endowment Fund. Their support of the endowment fund will assist the Society in its efforts to maintain a vigorous scientific program during its "second century of progress."

# INSTRUCTIONS FOR APPLYING FOR APS MEMBERSHIP

## CURRENT APPLICATION FORMS

Most issues of The Physiologist routinely carry one copy of the current application form (following). This form will serve for all categories of membership. Any member desiring to sponsor more than one applicant may use a Xerox copy of this form. Any application submitted on an out-dated form will be redone on the acceptable form.

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 attend to those instructions specific to their desired category.

## GENERAL INSTRUCTIONS

FOR ALL CATEGORIES:

Use only the current application form. Check the box indicating the category of membership for which you are applying. Use the SPECIAL INSTRUCTIONS for that category when filling out the form. Type the Application. Fill out all applicable spaces. Only completed applications will be reviewed.

Alien Residents. Alien residents of the U.S. 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.

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.

**DO NOT INCLUDE A CURRICULUM VITAE**

Send no reprints.

Deadline Dates: Completed applications received between February 1 and July 1 are considered for nomination by the Council at the Fall Meeting. Applications received between July 1 and February 1 are considered for nomination by the Council at the Spring Meeting. Applications are not complete until all materials, including sponsor's letters, are received.

QUALIFICATIONS (Except Students):

The Membership Advisory Committee uses the following five categories in 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 are responsible for physiology in another department. Relatively high ratings are given to people with positions in clinical departments and to people functioning as independent investigators in commercial or government laboratories.

3. Contributions to the Physiological Literature. This category is of major importance. The applicant's bibliography is evaluated on the basis of publications in major, refereed journals which are concerned with problems judged to be primarily physiological in nature. Emphasis is given to papers published as the result of independent research. Special note is taken of publications on which the applicant is sole author or first author.

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. Special Considerations. This category permits the Membership Advisory Committee to acknowledge unique accomplishments of an applicant. These might be excellence in a specific area, or unusual contributions to Physiology resulting from talents, interest or a 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 refereed journals. It should be clear that they have played a major role in some of this research. They should have a position in physiological research, teaching, administration or related area, other than a training position (Council, April 1984).

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 (Council, April 1984).

In April 1984, Council adopted: "any student who is actively engaged in physiological work which should lead to an advanced degree in physiology or related area, as attested by two regular members of the Society and who is a resident of North America, can qualify as a student member. No individual may remain in this category for more than five years, without reapplying."

SPONSORS:

Primary responsibility for membership rests with the two sponsors who must be regular members of the Society. Sponsors should discuss the appropriateness of the selected category of membership in this Society with prospective applicants.

Each sponsor should write an independent confidential letter about the candidate using the five categories listed above to evaluate the candidate. Furnish an original and seven copies to the Membership Secretary.

CHECK LIST:

1. Original copy of application signed by both sponsors.
2. Application on a current form, including the bibliography (1 original and 7 copies).
3. Mail the original, which has been signed by the two sponsors, plus 7 copies to:

   Membership Secretary
   American Physiological Society
   9650 Rockville Pike
   Bethesda, Maryland 20814

## SPECIAL INFORMATION AND INSTRUCTIONS

### FOR REGULAR MEMBERSHIP

Bylaws of the Society:

Article III, Section 2 - Regular Members. Any person who has conducted and published meritorious original research in physiology and who is a resident of North America shall be eligible for proposal for regular membership in the Society.

Duties and Privileges:

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. Sponsor New Members.
6. Can present orally only one contributed paper, but, may co-author and/or sponsor more than one contributed paper by a non-member at the Spring (FASEB) and the Fall Meetings of the Society.
7. Receive The Physiologist.
8. Receive Federation Proceedings, Public Affairs Newsletters and annual Membership Directory.
9. Subscribe to handbooks and periodicals published by the Society at membership rates.
10. Register to attend scientific meetings of the Federation and the APS Fall meeting at membership rates.
11. Participate in FASEB Member's Life Insurance Program, Disability Program and in Hospital Protection Plan. (For Residents of the United States, its territories or possessions).
12. Eligible to receive the Daggs Award.
13. Eligible to be selected as Bowditch Lecturer (Members under 40 years of age).

### FOR CORRESPONDING MEMBERSHIP

Bylaws of the Society:

Article III, Section 3 - Corresponding Members. Any person who has conducted and published meritorious research in physiology, who is presently engaged in physiological work and who resides outside of North America shall be eligible for proposal for corresponding membership in the Society.

Duties and Privileges:

1. Serve on Society Committees, Boards and Task Forces.
2. Serve as one sponsor of new Corresponding Members (One regular member must be the other sponsor of a new Corresponding Member).
3. Can present orally only one contributed paper, but, may co-author and/or sponsor more than one contributed paper by a non-member at the Spring (FASEB) and the Fall Meetings of the Society.
4. Receive The Physiologist.
5. Receive Federation Proceedings, and annual Membership Directory.
6. Subscribe to handbooks and periodicals published by the Society at membership rates.
7. Register to attend scientific meetings of the Federation and the APS Fall meeting at membership rates.

### FOR ASSOCIATE MEMBERSHIP

Bylaws of the Society:

Article III, Section 5 - Associate Members. Persons who are engaged in research in physiology or related fields and/or teaching physiology shall be eligible for proposal for associate membership in the Society provided they are residents of North America. Associate members may later be proposed for regular membership.

Duties and Privileges:

Same as for Regular Members except for the privileges of:

1. Holding Executive Office, or membership on certain committees.
2. Voting at Society Meetings.
3. Sponsoring New Members.
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.

### FOR STUDENT MEMBERSHIP

Not all questions on the application form may be appropriate – Please place NA next to any such questions.

Bylaws of the Society:

Article III, Section 7 - Student Members. Any student who is actively engaged in physiological work as attested by two regular members of the Society and who is a resident of North America. No individual may remain in this category for more than five years, without reapplying.

Duties and Privileges:

1. Present one contributed paper at the Spring (FASEB) and the Fall scientific meeting with the endorsement of the student's advisor.
2. Receive The Physiologist.
3. Subscribe to handbooks and periodicals at member rates.
4. Register to attend scientific meetings of the Federation and the APS Fall meeting at student rates.

**Submit original and 7 copies of application and supporting documents.**

APPLICANT'S LAST NAME _____

Date _____

THE AMERICAN PHYSIOLOGICAL SOCIETY
9650 Rockville Pike, Bethesda, MD 20814

# MEMBERSHIP APPLICATION FOR:

REGULAR ☐
CORRESPONDING ☐
ASSOCIATE ☐
STUDENT ☐

CURRENT MEMBERSHIP
CATEGORY; YEAR ELECTED _____

**See Instructions**

Name of Applicant: _____
First Middle Last

Mailing _____ Birth Date: _____

Address _____ Citizenship: _____

_____ Country of Permanent Residence:* _____

_____ Telephone No.: _____

* Alien residents of Canada and Mexico see General Instructions. Alien residents of U.S. enter Alien Registration Receipt Card number _____.

## 1. EDUCATIONAL HISTORY

| Dates | Degree | Institution | Major Field | Advisor |
|---|---|---|---|---|
| | | | | |

Doctoral Dissertation Title:
(if any)

Postdoctoral Research Topic:

## 2. OCCUPATIONAL HISTORY

Present Position:

Prior Positions:

| Dates | Title | Institution | Department | Supervisor |
|---|---|---|---|---|
| | | | | |

## SPONSORS

#1. Name: _____ #2. Name: _____

Mailing Address: _____ Mailing Address: _____

_____ _____

_____ _____

_____ _____

Telephone No. Zip Code Telephone No. Zip Code

I have read the guidelines for applicants and sponsors 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, under separate cover.

APPLICANT'S LAST NAME _____

3. **DESCRIBE YOUR PHYSIOLOGICAL TEACHING** – What percent of your time/effort is spent in teaching Physiology?_____

Describe in the space provided your teaching of physiology including course descriptions (content, format); supervision of pre-doctoral and post-doctoral students; special contributions (films, textbooks, etc.).

4. **INTEREST IN THE SOCIETY** – List any APS Meetings attended by date and check the appropriate box for any papers.

| SPRING (FASEB) | | | FALL (APS) | | |
|---|---|---|---|---|---|
| Date | Presented | Coauthor | Date | Presented | Coauthor |
| _____ | ☐ | ☐ | _____ | ☐ | ☐ |
| _____ | ☐ | ☐ | _____ | ☐ | ☐ |
| _____ | ☐ | ☐ | _____ | ☐ | ☐ |
| _____ | ☐ | ☐ | _____ | ☐ | ☐ |
| _____ | ☐ | ☐ | _____ | ☐ | ☐ |

List other scientific societies of which candidate is a member:

In the space provided state your interest in wanting to join the Society:

5. **SPECIAL CONSIDERATION** – Include any other contributions (Administrative, university, national service, awards and honors) that may be important to physiology.

6. **DESCRIBE YOUR RESEARCH** – What percent of your time/effort is spent in research?_____

Describe the fundamental physiologic questions in your research and how you have answered these questions. Limit the paragraph to the space provided.

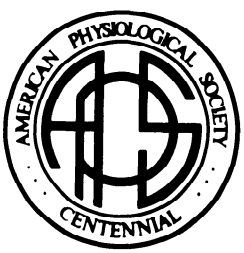
7. **BIBLIOGRAPHY** – Attach a list of your publications under the following categories:
   1. Complete physiological papers, published or accepted for publication.
   2. Physiological abstracts (limit to ½ page).
   3. Other papers not primarily physiological (limit to ½ page).

The entire bibliography should not exceed 2 pages. Give complete titles and journal references with inclusive pagination. Use the bibliographic form found in the Society's journals. List authors in the order in which they appear in the publication.

# 37th Annual Fall Meeting of the American Physiological Society

Clarion Hotel
New Orleans, Louisiana

October 5–9, 1986




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

### APS Business Meeting
Wednesday, October 8, 5:15 PM–6:15 PM
Clarion Hotel, Grand Ballroom B

### Bowditch Lecture
Wednesday, October 8, 4:15 PM–5:15 PM
Clarion Hotel, Grand Ballroom B

### Comparative Physiology Section Luncheon
Wednesday, October 8, 12 Noon–1:30 PM
Clarion Hotel, Mimosa Room

### Teaching of Physiology Section Meeting
Monday, October 6, 5:00 PM–6:00 PM
Clarion Hotel, Audubon C

### APS Public Affairs Workshop
Wednesday, October 8, 9:00 AM–10:30 AM
Clarion Hotel, Audubon D

### Society for Experimental Biology and Medicine Council Dinner and Meeting
Monday, October 6, 6:00 PM–10:00 PM
Clarion Hotel, Fleur-de-Lis 6
(By invitation only)

### Evening Social Events

*Opening Reception*
Sunday, October 5, 8:00 PM–10:00 PM
Clarion Hotel, Sixth Floor Pool Deck

*Open House and Reception at LSU and Tulane*
Monday, October 6, 5:00 PM–7:00 PM

*APS Past President's Address and Societal Banquet*
Tuesday, October 7, 6:45 PM–10:00 PM
Clarion Hotel, Grand Ballroom A
*Topic:* The APS and Its Centenary Year
*Speaker:* Howard E. Morgan

*Mississippi River Cruise and Jazz Band*
Wednesday, October 8, 7:00 PM–9:30 PM
Bayou Jean Lafitte

## Symposia, Tutorial and Workshop Sessions

### Monday AM
Symposia
- Theme I: Neuro humoral regulation of water and electrolyte balance. Session I: Neuropeptides: angiotensin and vasopressin
- Theme II: Physiological limitations to performance. A comparative approach. Session I
- NMR spectroscopy as an investigative technique in physiology

### Monday PM
Symposia
- NMR spectroscopy as an investigative technique in physiology

### Tuesday AM
Symposia
- Theme I: Session II: Neural and humoral control of kidney functions
- Theme II: Physiological limitations to performance. A comparative approach. Session II
- Endothelium-derived vasoactive factors

### Tuesday PM
Symposia
- Endothelium-derived vasoactive factors reactivity

Workshop
- Integrative study in physiology and medicine

### Wednesday AM
Symposia
- Theme I: Session III: Neural humoral regulation of electrolytes and water balance at the microcirculation
- Theme II: Operation Everest. Session I: Limitations to performance at altitude

### Wednesday PM
Workshop
- Integrative study in physiology and medicine

Tutorials
- Cellular mechanisms mediating tubuloglomerular feedback control of the GFR
- Cellular and biochemistry mechanisms of renal injury
- Cellular mechanisms regulating renin release

### Thursday AM
Symposia
- Theme I: Session IV: Neural humoral mechanisms of thirst and salt appetite
- Theme II: Operation Everest. Session II: Limitations to performance at altitude
- Perspectives on immunophysiology

### Thursday PM
Symposia
- Pathophysiology of infection and trauma

Workshops
- Integrative study in physiology and medicine

# Sessions and Symposia with Associated Abstracts

# A Workshop on Integrative Study in Physiology and Medicine APS Fall Meeting, New Orleans, Louisiana October 7–9, 1986

**Joseph Engelberg and David C. Randall**
*Department of Physiology and Biophysics, Albert B. Chandler Medical Center, University of Kentucky, Lexington, Kentucky 40536-0084*

The Fall Meeting of the American Physiological Society in New Orleans, Louisiana, will include a workshop entitled "Integrative Study in Physiology and Medicine." This is the second such workshop (the first having been held at the 1984 Lexington, KY, meeting) in what we hope will become an annual event. The purpose of these workshops is to provide an opportunity to discuss the functioning of living organism as an integrated system. The workshop will utilize a case study describing multiple disease processes in a 30-year-old diabetic woman as a focal point for discussion; the case is abstracted below and contains many points relevant to the symposium "Neurohumoral Regulation of Water and Electrolyte Balance."

By way of background, physiologists have traditionally been "natural philosophers," pioneers of broad, integrative systems approaches to the study of living processes. Their approach has been rooted in the very nature of biological organisms, as is evident in the published works of great investigators such as Claude Bernard and Sir Charles Sherrington. This tradition, however, has been treated very casually in our time to the point that it seems in danger of extinction. This is reflected in the often-stated concern that the contemporary student's education focuses around very narrowly defined problems and involves little breadth of understanding.

Medical case histories can serve as natural integrative devices for workshops such as these, since during a major illness the initial pathological perturbation spreads itself over every imaginable aspect of biological function via the interactive control mechanisms that attempt to maintain homeostasis throughout the course of the disease. Furthermore, the case history can serve as a basis for discussion of phenomena from the cellular through the organ, organ-system, whole-body, and social levels. Integrative study leads to a broader understanding of general and cellular physiology.

The workshop sessions will be loosely structured. Their function will be to stimulate wide-ranging and creative discussion among participants. Two exploratory sessions of up to two hours' duration will be held on October 7th and 8th; the final session on Thursday, October 9th, will be used to develop an overview of the case and to discuss methods of integrative study. Members of the organizing team will be present at all three sessions, but their responsibility will be limited to outlining the case, briefly summarizing insights from previous sessions, and serving as catalysts for discussion.

Those interested in attending the workshop are encouraged to read the entire case as originally published in the *New England Journal of Medicine*. A brief summary follows. Normal values for clinical variables are given in parentheses.

Case Study: A 30-year-old mentally retarded diabetic woman who is brought to the hospital in a coma.
Source: *New England Journal of Medicine* 279: 819–828, 1968.
Normal values: in parentheses.

A thirty-year-old mentally retarded diabetic woman was found in her room, cold and totally unresponsive. She had had eight pregnancies. Three years previously, on admission to another hospital for the last pregnancy, diabetes mellitus was discovered, but no treatment was prescribed. On hospital examination the patient appeared moribund and did not respond to painful stimuli; the tendon reflexes were absent. Her rectal temperature was below 93°F on admission, and 95°F eight hours later.

She was severely dehydrated. The cervical veins were flat, and the carotid and peripheral pulses were normal. Examination of the lungs, heart and abdomen was negative. The urine gave a ++++ test for glucose and acetone (zero is normal). The serum acetone was + (zero normal) at a dilution of 1:64.

The pulse was 80. The blood pressure was 60 systolic by palpation. An electrocardiogram demonstrated a normal sinus rhythm.

Arterial blood:
partial pressure of oxygen 99 mm Hg (96–100)
partial pressure of carbon dioxide 30 mm Hg (35–45)
pH 6.86 (7.35–7.45)
The plasma glucose was 1,250 mg/dl
(fasting: 70–100)
amylase 38 Russell units (4–25)
sodium 128 mEq/l (136–145)
potassium 1.8 mEq/l (3.5–5)
chloride 106 mEq/l (100–106)
carbon dioxide 7 mEq/l (26–28)
calcium 8.3 mEq/dl (8.5–10.5)
urea nitrogen 24 mg/dl (8–25)
protein 4.4 gm/dl (6–8)
albumin 2.5 gm (4–5)
globulin 1.9 gm/dl (2–3)
barbiturate 0.4 mg/dl
(0; coma level: 11)
The hematocrit was 35% (40–48)
and the white-cell count 11,200 (5000–10,000)
with 39% neutrophils (57–67)
21% band forms (3–5)
21% lymphocytes (25–33)
17% monocytes and (3–7)
2% metamyelocytes (0).

During the first twenty-four hours, 700 units of insulin, 14 liters of fluid and 400 mEq of potassium chloride were administered intravenously. Her blood pressure rose to 100 systolic, 60 diastolic, central venous pressure 10 cm of saline, with increasing urinary output.

On the second hospital day the blood pressure began to fall despite the continuous infusion of large volumes of fluid and plasma. The hematocrit was 34% (40–48). Transfusions of fresh whole blood were given, and penicillin G, oxacillin and chloramphenicol were administered. Isoproterenol was added to the regimen, but the blood pressure became unobtainable. Marked abdominal distention developed. Aspiration of the stomach

yielded a small amount of brown green liquid that gave a ++++ guaiac test (showing the presence of blood).

The potassium was 5.5 mEq/l (3.5-5) and the glucose 630 mg/dl (fasting: 70-100);

the test for serum acetone was negative.

Bradycardia developed in the evening, followed by cardiac arrest. The patient was reviewed by countershock and the blood pressure rose to 90 systolic, 60 diastolic.

Plasma glucose 360 mg/dl (fasting: 70-100);
sodium 135 mEq/l (136-145),
potassium 2.8 mEq/l (3.5-5).

Two liters of gastric contents were aspirated. X-ray films showed that the large bowel was dilated and filled with fecal material; the liver was normal in size. Digoxin was administered. The temperature ranged between 99 and 101°F. The patient remained unresponsive, though she moved both arms in response to painful stimuli. By the end of the second hospital day the central venous pressure had risen to 24 cm of saline; the blood pressure was 100 systolic, 60 diastolic.

On the third hospital day the blood pressure was 100 to 110 systolic, 60 to 80 diastolic and the pulse 105 to 120/min. The urinary output was 100 ml per hour (40-50). The abdomen was diffusely tender; palpation disclosed a nontender, soft mass, with its lower margin at the left iliac crest. Cultures of blood taken on admission grew out gram-negative rods and gram-positive cocci that were subsequently identified as klebsiella and Group B streptococci, respectively. A spinal-fluid culture was negative. Culture of urine taken on admission yielded abundant yeast organisms.

On the fourth hospital day the patient's mental status improved; she could move her fingers and toes on command.

Plasma glucose 309 mg/dl (fasting: 70-100)
urea nitrogen 34 mg/dl (8-25)
sodium 129 mEq/1 (136-145)
potassium 4.0 mEq/l (3.5-5)
chloride 98 mEq/l (100-106)
carbon dioxide 20 mEq/l (26-28)
White-cell count 3700 (5000-10,000).

Chloramphenicol was discontinued, and kanamycin was begun. A specimen of urine (3000 ml) contained 5800 mg protein (<150).

Cardiac arrest recurred on the sixth hospital day; the patient was resuscitated with external cardiac massage. An electrocardiogram demonstrated a sinus rhythm, with marked loss of R waves in the anterior leads and loss of voltage in the lateral leads; the T waves were flat in all the leads.

An x-ray film of the chest revealed a small left pneumothorax; a tube was inserted, and the lungs expanded. The lungs were clear, with no vascular congestion. The glutamic oxalacetic transaminase (SGOT) was 190 units (10-40). The blood pressure was maintained between 90 and 100 systolic.

On the next day the temperature rose to 105°F. No rales or cardiac murmurs were audible.

On the eighth hospital day the patient was deeply obtunded. An electroencephalogram demonstrated barely perceptible activity.

Plasma SGOT 150 units (10-40)
lactic dehydrogenase (LDH) 600 units (60-100)
calcium 5.8 mg/dl (8.5-10.5)
phosphorus 2.6 mg/dl (3-4.5)

On the tenth hospital day scattered punctate skin lesions with vesicular centers on necrotic erythematous bases appeared. Aspirated vesicular fluid contained large numbers of gram-negative rods; cultures of the skin lesions, the blood and the urinary catheter grew out *Pseudomonas aeruginosa*. Kanamycin was discontinued, and colistin was begun.

On the following day the temperature was 105°F; the white-cell count was 5300 (5,000-10,000). Neurologic examination disclosed no change.

On the twelfth hospital day the temperature was 104°F; the blood pressure was 75 to 80 systolic.

The patient died on the thirteenth hospital day.


## American Physiological Society Endowment Fund

The APS Endowment Fund was established in 1977 to support programs for the development of physiologists and physiology; to encourage communication with other disciplines of science and the public; and to foster scientific and cultural relations with other parts of the world.

The APS Endowment Fund was established to encourage tax-deductible contributions or bequests to the society at any time and in any amount, for specific or general purposes. Upon request, the society will provide to a donor or institution contributing a memorial gift a replica of the plaque bearing the name of the individual living or deceased in whose honor the gift was made. The family of, or the individual being honored by a donation to the fund, will be advised formally of the donor's name, unless the contributor specifically requests that the donation be anonymous.

Donations to the APS Endowment Fund or queries should be addressed to 9650 Rockville Pike, Bethesda, MD 20814.

4.1

POLYMORPHONUCLEAR NEUTROPHIL FUNCTIONAL KINETICS AFTER PNEUMOCOCCAL CHALLENGE. A PROPOSED MECHANISM OF PULMONARY LEUKOSTASIS IN PNEUMOCOCCAL INFECTIONS. C. K. Jutila*, M. A. Jutila*, R. E. Crowell*, T. W. Chick*, D. E. Van Epps*, and W. P. Reed* (SPON: S. Wood). Research Service, VA Medical Center, Albuquerque, NM 87108.

Pneumococcal (PNC) infections continue to cause significant morbidity and mortality despite immunization and appropriate antibiotic use. Pulmonary leukostasis with neutropenia and profound shock are seen in humans and experimental animals with fatal PNC infections. The present study was designed to determine functional changes in polymorphonuclear neutrophils (PMNs) and to evaluate the role of the alveolar macrophage (AM) in pulmonary leukostasis after PNC injection in dogs. Blood samples from the pulmonary artery (PA) and femoral artery (FA) were obtained pre-injection and 15 to 90 minutes after PNC injection; cell counts and superoxide anion production were compared to determine transpulmonary differences. Serial bronchoalveolar lavages (BAL) were performed and differential counts of cells recovered were evaluated; chemotactic activity of recovered AMs was assayed. After sonicate injection we found chemotactic activity for PMNs in both the AMs and supernatants obtained from the BAL along with increasing numbers of PMNs in successive BAL samples. Granulocytopenia with a depression in superoxide anion production, most pronounced in the FA, was noted by 15 minutes post-sonicate injection. Our results suggest that, in response to PNC sonicate, chemotactic factors are produced in the lung by the AM and are responsible for the pulmonary leukostasis with neutropenia seen in humans and animals challenged with PNC.

4.2

C3A CAUSES PREFERENTIAL CONSTRICTION OF HILAR COMPARED TO MAIN PULMONARY ARTERIES AND IS HISTAMINE-DEPENDENT. R. Crowell*, W. Reed*, D. Van Epps*, D. Chenoweth*, T. Chick*, J. Leach. Research Service, VA Medical Center, Albuquerque, NM 87108

Products of the complement (C) cascade may have direct effects on pulmonary vascular tissue and contribute to the pulmonary vasoconstriction in states of C activation. We studied the effects of C3a, a C-derived vasoactive peptide, on isolated rabbit hilar (HPA) and main pulmonary arteries (MPA). C3a elicited concentration-related constriction of HPA ($10^{-8}$M - $5x10^{-7}$M), but minimal response in MPA at all concentrations tested. The difference between HPA and MPA responses was significant ($p < .05$, Student's paired t-test). To evaluate HPA desensitization to C3a, the peptide was reapplied at 60 minutes in some tissues and at 120 minutes in others. All tissues consistently exhibited less constriction at 60 minutes than observed with initial exposures, but mean responsiveness at 120 minutes was not different. However, there was significant variability of the repeat C3a responses at 120 minutes not seen with other agonists exposed to the same tissues (norepinephrine: $5x10^{-6}$M, histamine: $10^{-4}$M), with a range of 50% to 300% of the original constriction. Histamine contribution to the HPA response to C3a was determined by exposing the tissues for 30 minutes prior to C3a application to pyrilamine (PYR; $1x10^{-5}$ M), an H-1 receptor antagonist. PYR reduced the HPA response to C3a by 70-85%. We conclude that: 1) isolated rabbit PA responses exhibit regional variability to C3a over a range of concentrations; 2) C3a desensitizes HPA for at least 60 minutes, but the tissue demonstrates variable recovery within 120 minutes; and 3) HPA responses to C3a are histamine-dependent.

4.3

LOW-DOSE AND HIGH-DOSE MECLOFENAMATE (Meclo) ABLATE ETHANOL (ETOH) INDUCED PULMONARY VASOCONSTRICTION. W.H. Drummond, and Diana Lyles*. Univ. of Florida, Department of Pediatrics, Neonatology Division, Gainesville, FL 32610

Low dose ETOH (.03 ml/kg/min, IV) causes severe pulmonary and mild systemic vasoconstriction which is blocked by 8 mg/kg indomethacin, po (Drummond; Circ 68;III:404, 1983). Doekel (J Appl Phys 44:76, 1978) noted a similar ↑ in pulmonary vascular resistance (PVR), in dogs, which was not changed by meclo (2 mg/kg, IV).

To evaluate the discrepancy, 8 lambs were chronically instrumented for measurement of systemic (SAP), pulmonary (PAP), left atrial (LAP) pressures, and pulmonary blood flow (=cardiac output). The ductus arteriosus was ligated. Systemic vascular resistance and PVR were calculated. The lambs were studied at age 8 to 37 days at 3 different times with ETOH .03 ml/kg/min, ETOH + Meclo at 2 mg/kg, IV or 8 mg/kg, IV. Data were analyzed by ANOVA. ETOH alone ↑'d PAP (23 ± 3 vs 42 ± 5 mmHg, $p<.001$) and PVR (.13 ± .03 vs .38 ± .1 units, $p<.03$). No other circulatory measurements changed. Meclo 2 mg/kg blunted PAP rise (22 ± 3.5 vs 34 ± 3.7 after ETOH, p=NS) and PVR (.18 ± .04 vs .29 ± .05, p=NS) change. Meclo 8 mg/kg completely obliterated the pulmonary vascular response (PAP: 24 ± 2.8 vs 26 ± 3.2 mmHg; PVR: .18 ± .03 vs .18 ± .03 units). Thus, ETOH appears to affect the pulmonary circulation via a prostaglandin-dependent mechanism. The discrepancy between dogs' and lambs' responses may relate to species, age, or technical differences.

4.4

PERINATAL PULMONARY PROSTAGLANDIN (PG) $H_2$ METABOLISM. J.A. Bellan*, S. Cassin, M.D. Kerstein*, P.J. Kadowitz*, A.L. Hyman, D.S. Rush* and D.B. McNamara*. Tulane Medical School, New Orleans, LA 70112, and Univ. of Florida College of Medicine, Gainesville, FL 32610

Thromboxane $A_2$ (TX), $PGI_2$, and $PGE_2$ are implicated in the regulation of blood flow and airway tone in the late-fetal (F), neonatal (N), and adult (A) lung. GSH is the required cofactor for GSH-dependent $PGE_2$ isomerase, and is reported to decrease in the lung around the time of birth. Microsomal fractions (Mf) were isolated from whole lung tissue of F, 8-day N, and A goats. Varied concentrations of Mf protein and of 1-$^{14}$C $PGH_2$ were incubated ± 2 mM GSH. Products were separated and quantified by thin layer radiochromatography. $PGE_2$ synthesis in F and N Mf was similar and much higher than in A. TX synthesis was greatest in A Mf, and similar in F and N. GSH decreased TX synthesis in all Mf; F and N were more sensitive to this effect. GSH decreased $PGI_2$ synthesis in F and N Mf, but the magnitude of this effect was less than that on TX synthesis. In perinatal Mf, $PGI_2$ synthesis was greater than TX synthesis at low $PGH_2$ concentration and in the presence of GSH, but TX synthesis was increased relative to $PGI_2$ at higher $PGH_2$ concentrations in the absence of GSH. Patterns of $PGH_2$ metabolism were very similar in F and N Mf, suggesting that perinatal changes in pulmonary $PGH_2$ metabolism may result from variations in factors such as GSH and substrate concentrations. However, at identical concentrations of Mf protein, GSH, and $PGH_2$, A Mf differ from F and N.

4.5

THE EFFECTS OF ETHANOL ON PULMONARY VASCULAR SYMPATHOMIMETIC ACTIVITY. R.J. Porcelli and P.C. Devine*. VAMC at Northport New York, 11768.

Recent studies have demonstrated that ethanol (ETOH) augments the acute hypoxic pressor response (AHPR) in a dose-dependant fashion and this occurs with coincident increases in plasma catecholamines (Fed. Proc. 45:161,1986). Although the relation between ETOH, AHPR and circulating catecholamines are uncertain, the direct effects of ETOH on the pressor responses to the catecholamines may be important to this understanding. The present study, therefore, examined the effects of ETOH on the pulmonary pressor responses to norepinephrine (NE) and phenylephrine (PE) in the isolated blood-perfused lung. NE raised pulmonary vascular resistance (Rpv) by 34±3% during control and as plasma ETOH increased to 42±1 mg/dL and to 138±6 mg/dL the ΔRpv was enhanced to 47±5%* and 55±18%*, resp.(n=8). These observations resulted from greater absolute changes in Rpv to NE with ETOH which averaged 0.26±0.05 torr.$ml^{-1}$.min vrs 0.15±0.01 torr.$ml^{-1}$.min during control. In contrast, the control ΔRpv to PE of 29±3% was not altered by low or high ETOH levels (22±4%ΔRpv @ 35±1 mg/dL and 39.6%ΔRpv @ 145±8 mg/dL, resp. n=8). These data suggest that ETOH may augment pulmonary sympathetic activity by increasing the ΔRpv to NE. This effect may not involve a change in either overall or α-adrenergic contractility (re PE results) but ETOH may enhance both the AHPR and the pressor response to NE in a manner that is similar to β-adrenergic blockade. *=p<0.05.
Supported by the Veterans Administration, Washington, D.C.

4.6

EVIDENCE FOR VASCULAR DOPAMINE RECEPTOR ($DA_1$) INVOLVEMENT IN MODULATION OF PULMONARY VASCULAR TONE. Mark J. Polak* and Willa H. Drummond. University of Florida, Department of Pediatrics, Neonatology Division, Gainesville, FL 32610

Fenoldopam (Fen) is a highly selective $DA_1$ agonist. Previous studies from our lab using chronically instrumented lambs have shown increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) with infusions of Fen. This ↑ in PVR is dose dependent, additive with hypoxia, and minimally attenuated by alpha adrenergic blockade. To determine the extent of pulmonary $DA_1$ receptor involvement in this ↑ in PVR, a series of experiments was conducted using infusions of Fen alone and in the presence of SCH-23390, a new, selective $DA_1$ antagonist.

12 lambs, aged 5-28 days, have completed 24 experiments using a cross-over design. Infusion of Fen alone causes a slight increase in cardiac output with no change in heart rate, or systemic artery pressure. FEN increased PAP ($p<0.05$) in a dose dependent manner. Calculated values of systemic vascular resistance (SVR) decreased by 15% while PVR increased by 73% at the highest doses of Fen. Fen given with a constant infusion of SCH-23390, showed a marked attenuation of the Δ PVR and Δ PAP ($p<0.05$ at the highest dose of Fen) without attenuation in other parameters.

We conclude that the pulmonary vasoconstriction noted with Fen is at least partly the result of a previously unrecognized dopaminergic mechanism that may act as a modulatorof pulmonary vasomotor tone in lambs.

## 4.7

INFLUENCE OF FOREBRAIN STIMULATION ON ARTERIAL EPINEPHRINE LEVELS. Albert L. Hyman, C. Dempsey, C. Fontana, J. Miotke*, R.W. Richardson and P.J. Kadowitz*. Tulane Medical School. New Orleans, LA 70112

Forebrain stimulation has been shown to elicit a biphasic response in the pulmonary vascular bed when vascular tone was maintained at a high steady level. The biphasic response was composed of an initial constrictor component followed by an earlier and then latter sustained dilator response. The late sustained dilator response was blocked by propranolol or ICI118,551 suggesting that it was due to beta-2-adrenoceptor activation. To determine if circulating epinephrine was mediating the sustained dilator response, arterial levels of epenephrine were measured during the control period andprior to the onset of the vasodilator response. In these experiments arterial epinephrine levels increased from 226 ± 96 to 4629 ± 877 pg/ml. These data suggest that the sustained vasodilator response is mediated by circulating epinephrine which is released from the adrenal medulla by forebrain stimulation. These data support the concept that the pulmonary circulation can be actively regulated by discrete centers in the brain.

## 4.8

CALCIUM ANTAGONIST BLOCKS RESPONSES TO ALPHA-1 AND ALPHA-2 AGONISTS IN THE PULMONARY AND MESENTERIC VASCULAR BEDS OF THE CAT. Philip J. Kadowitz*, Howard L. Lippton*, William M. Armstead* and Albert L. Hyman. Tulane Medical School, New Orleans, LA 70112.

The influence of calcium entry blockade on vasoconstrictor responses to alpha-1 (α-1) and alpha-2 (α-2) adrenoceptor agonists was investigated in the feline mesenteric and pulmonary vascular bed. Under conditions of controlled blood flow, phenylephrine and methoxamine, α-1 agonists, and UK14304 and BHT933, α-2 agonists, increased mesenteric arterial and lobar arterial perfusion pressures in a dose-dependent manner. After treatment with nisoldipine, mesenteric and pulmonary vasoconstrictor responses to phenylephrine and methoxamine or UK14304 and BHT933 were significantly reduced. The blocking effects of the calcium antagonist was reversible and responses to the α-1 and α-2 agonists returned toward control values 60 min after infusion of calcium entry antagonist. Nisoldipine inhibited vasoconstrictor responses to Bay k 8644, a nifedipine analog, which promotes calcium entry. The present data suggest that similar sources of calcium are required for vasoconstriction elicited by α-1 and α-2 adrenoceptor agonists in the pulmonary and mesenteric vascular beds of the cat. In addition these data suggest that nisoldipine and Bay k 8644 interact at a common site on the cell membrane to regulate transmembrane calcium influx.

## 4.9

PULMONARY DISPOSITION OF PROPRANOLOL IN THE NORMAL AWAKE SHEEP. R.E. Howell*, P.N. Lanken*, S.M. Albelda* and A.P. Fishman. University of Pennsylvania, Philadelphia, PA 19104

Although it is known that the lung extracts propranolol from the plasma, the mechanism of this process is not clearly understood. We characterized the single-pass pulmonary extraction of $^{3}$H-propranolol and its intrapulmonary distribution in 28 normal awake sheep. There was a direct relationship between the extraction of propranolol (0.75 ± 0.04) and the single-pass pulmonary retention of propranolol (38 ± 5%). Propranolol extraction showed no evidence of saturation despite increasing the dose from 1 ng/kg up to 0.1 mg/kg or by pretreatment with propranolol, and was unaltered by isoproterenol. Also, propranolol extraction remained constant after increasing cardiac output 2-3 fold by treadmill exercise, and was unreduced after decreasing lung capillary surface area 60% by injecting into a lobar artery. Propranolol rapidly appeared in lung lymph during the first sixty minutes after intravenous administration, and reached a lymph-to-plasma concentration ratio of 1.4. Propranolol also was found in bronchoalveolar lavage five minutes after intravenous administration, and was estimated to be 125 times more concentrated in bronchoalveolar fluid than in plasma. We conclude that the pulmonary extraction and retention of propranolol in vivo results from a flow-limited diffusion of propranolol into the lung, that propranolol readily crosses the alveolar-capillary barrier, and that propranolol may become concentrated in lung interstitial and alveolar fluid after injection.

## 4.10

GLUCOCORTICOID-INDUCED VASODILATION IN THE IPL OF THE CAT. M. Cutaia; P.Friedrich*. VA Medical Center, Northport, NY 11768

Glucocorticoids(G) are known modifiers of systemic blood flow. Little is known of their effects on the pulmonary circulation. We examined the acute effects of hydrocortisone (Hy), methylprednisolone(M) and dexamethasone(D) on lobar hemodynamics when vascular resistance(Rpv) was normal under constant flow conditions(n=25). Each animal received one hormone by a cumulative dosing method; perfusate dose ranges: Hy,1.6-106x10$^{-5}$M; M,1.6-107x10$^{-5}$M; D,1.5-98x10$^{-5}$M. Maximum vasodilator responses (ΔP) were:-3.3±0.6(n=12);-2.6±0.5(n=6);-4.4±0.8 (n-7) torr for Hy,M,D, respectively. ΔP to hormones demonstrated a significant correlation with baseline lobar pressure(P) (ΔP=-.35P±2.44,r=0.63,p<0.001). In a separate series (n=7), we compared the responses to single doses of M (107x 10$^{-5}$M) under 4 conditions: normal Rpv(control) vs. when Rpv↑ with histamine(H), serotonin(S) and acute hypoxia(AH). ΔP for each condition:

| M(Cont) | Hist/M | S/M | AH/M |
|---|---|---|---|
| -1.3±0.4 | 33±4.2/-4.9±1.8 | 10.4±1.3/-3.3±0.8 | 7.3±1.5/-6.9±2.2* |

There was no correlation of ΔP to H,S,AH and ΔP to M infused during each condition. We conclude: 1) C produce vasodilation when Rpv is normal; 2) the magnitude of these responses varied directly with P; 3) AH potentiates these responses independent of the ↑Rpv during AH.
*p<0.05 vs. M(Cont). Supported by the VA.

## 4.11

CHANGES IN PROTEIN FLUX ACROSS AN ENDOTHELIAL CELL MONOLAYER DUE TO MODULATION OF CELL VOLUME. J.M. Shepard, H.K. Kimelberg*, S.K. Taylor*, and A.B. Malik. Albany Medical College, Albany, NY 12208.

We measured protein flux across a cultured endothelial cell monolayer with solutions of varying osmolality present to induce cell volume alterations. Bovine pulmonary artery endothelium was grown to confluence on gelatinized polycarbonate filters, and the flux of $^{125}$I-albumin was measured under pure diffusion conditions. The solution bathing the cells was a HEPES-buffered balanced salt solution with 0.5% albumin (iso-osmotic, 292 mOsmol/kg) that was made hypotonic by the removal of 100 mM of NaCl (hypo-osmotic, 118 mOsmol/kg), or made hypertonic by the addition of 200 mM Mannitol (hyper-osmotic, 492 mOsmol/kg). These changes resulted in a sustained shrinkage of about 66% for the hypertonic and an initial swelling of about 100% for the hypotonic media, as measured in attached cells by the volume of distribution of [$^{14}$C] urea. In hypotonic media the cell volume regulated back to control levels within 30 minutes. The protein fluxes at the different osmolalities are: (means ± S.D., *p<0.01)

| Exp.# | Iso | Hypo | Hyper | |
|---|---|---|---|---|
| 1 | 0.38±0.12 | 0.20±0.03* | 0.58±0.11* | (n=4) |
| 2 | 0.31±0.09 | 0.30±0.07 | 0.45±0.08* | (n=8) |
| 3 | 0.40±0.09 | 0.33±0.06 | 0.56±0.09* | (n=8) |

We conclude that changing the volume of endothelial cells using different osmotic environments affects junctional permeability as reflected by the change in protein flux. (HL-32418)

## 4.12

CIGARETTE SMOKE EXTRACT INCREASES PERMEABILITY OF PULMONARY ENDOTHELIAL MONOLAYERS IN CULTURE. W.E. Holden, J.M. Maier*, D.E. Griffith*, and M.R. Malinow. Portland VAMC & Ore. Regional Primate Research Ctr., Portland, Ore. 97207

Mechanisms of smoking-induced vascular disease are poorly understood, but increased endothelial permeability (EP) is an early feature of vascular injury and smoking increases epithelial permeability. To study effects of smoking on EP, we prepared a smoke extract (Smoke) by bubbling cigarette smoke in dimethyl sulfoxide (DMSO)(1 cigarette/ml). We compared effects of Smoke to calcium ionophore (C) which causes increased EP. Pig pulmonary artery endothelial cells were grown to confluent monolayers on polycarbonate filters (5 μ) coated with gelatin and fibronectin. Confluency was assessed by appearance and screening leakage of medium (RPMI) over 60 min. Fatty acid-free 1% bovine serum albumin (BSA) was placed on the luminal surface and flux of BSA across the monolayer/filter was measured over 30 min before (Bef) and after (Aft) a 30 min exposure to medium alone or 1% solutions of Smoke, carrier (DMSO), or C (5x10$^{-6}$M or 5x10$^{-5}$M). Only monolayers exposed to C (5x10$^{-5}$M) released increased LDH and appeared disrupted. Results (% change ± SEM from Bef to Aft):

| Medium | DMSO | Smoke | C (5x10$^{-6}$M) | C (5x10$^{-5}$M) | |
|---|---|---|---|---|---|
| 9 ± 3 | 8 ± 2 | 29 ± 3** | 32 ± 7** | 114 | (** p<.01 vs. |
| n=7 | n=7 | n=8 | n=5 | n=2 | Medium) |

Cigarette smoke extract increases EP to albumin with magnitude of effect similar to C (5x10$^{-6}$M).

4.13

NO DETECTABLE GRAVITY-INDEPENDENT BLOOD FLOW GRADIENTS IN DOG LUNG. G Nicolaysen, J Shepard, M Onizuka*, T Tanita* and NC Staub. Cardiovas Res Inst and Dept of Physiol, University of California, San Francisco, CA and Dept of Physiol, University of Oslo, Norway.

Hakim (FED PROC 4:919, 1984) reported a large hilar-to-peripheral, gravity-independent gradient of blood flow in 3 anesthetized dogs using single photon emission computerized tomography (SPECT), after i.v injection of radioactively-labeled albumin macroaggregates. The SPECT method requires a complex computer reconstruction of the lung image. In six anesthetized dogs we directly measured radioactive macroaggregate distribution in frozen lung slices. We injected 300 µCi of 111In-labeled albumin macroaggregates (20 µm diameter) i.v. over 1 min. At 5 min, we killed the dogs, opened the chest, inflated the lungs and froze them at constant alveolar pressure = 12 cmH20. In a cryostat, we sliced the lungs horizontally or vertically (1 each/dog). We divided each slice into three or four concentric rings and measured radioactivity in each ring [cts/(g x min]. The data are summarized in the table (mean ± 1 SD for each ring).

| Outer Ring | 2nd Ring | 3rd Ring |
|---|---|---|
| 711 ± 136 | 724 ± 116 | 765 ± 143 |

There was no trend for a central-to-peripheral gradient of blood flow distribution by analysis of variance, although there was the expected gravitational gradient from top to bottom. [Supported in part by HL25816 (Program Project) and HL36024].

4.14

DO CUFFED FLOW PROBES ALTER PULMONARY HEMODYNAMICS? Brydon J.B. Grant, Linda J. Paradowski* & James M. Fitzpatrick*. Dept. of Medicine, SUNYAB, Buffalo, NY 14215.

Cuffed electromagnetic flow (EMF) probes limit lateral wall motion of vessels locally which may cause hemodynamic changes. An EMF probe (Statham) was placed around the main pulmonary artery in seven anesthetized dogs. Although there were no changes of heart rate, systemic blood pressure, mean pulmonary arterial (PA) pressure, right ventricular end-diastolic pressure, or in mean PA flow to the left lower lobe which was used as an index of cardiac output, PA pulse pressure increased from 17.8 to 21.9 $cmH_2O$ ($p<0.04$) and mean right ventricular pressure increased from 23.2 to 25.9 $cmH_2O$ ($p<0.0005$). In addition, input impedance was calculated from measurements of PA pressure and flow in seven anesthetized cats. Impedance calculated from flow measured with a EMF probe was compared with impedance calculated from flow measured with a large ultrasonic flow probe (Transonics) which did not limit lateral wall motion. There were no significant differences in input resistance, characteristic impedance or PA compliance which were estimated from the input impedance. We conclude that the constraining effect of the EMF probe does affect right ventricular afterload, and that the measured input impedance may not reflect the entire right ventricular afterload. (Supported by RCDA HL-01418, the Whitaker Foundation, AHA and W Palm Beach Chapter).

4.15

EFFECT OF EDEMA ON LUNG SEGMENTAL VASCULAR RESISTANCE IN LAMBS DETERMINED BY MICROPUNCTURE. J. Usha Raj and Priscilla Chen*, Harbor-UCLA Medical Center, Torrance, CA 90509

To determine the mechanical effects of lung edema on the pulmonary circulation, we determined the longitudinal distribution of vascular pressures in 26 isolated blood perfused lungs of lambs with varying degrees of hydrostatic edema. We held constant alveolar and venous pressures (7 and 8 $cmH_2O$, respectively) as well as lung blood flow (540±107 ml/min). Papaverine in the perfusate prevented active vasomotor changes. We micropunctured 20-80 µm subpleural arterioles and venules to measure pressure by the servonull method. We found that alveolar edema developed after 80±13% of initial weight gain, without any change in total or segmental pressure drops. With continued edema formation, after 148±97% of initial weight gain, total vascular resistance increased. Vascular pressure drops ($cmH_2O$) are shown (mean ± SD).

| | Total | Arteries | Microvessels | Veins |
|---|---|---|---|---|
| Baseline | 22.1±1.4 | 4.1±3.2 | 9.2±2.9 | 9.1±1.2 |
| Severe edema | 37.2±4.5 | 12.2±4.0 | 20.1±4.1 | 7.2±1.6 |

With severe edema, regional distribution of blood flow in the lung determined by radiolabeled microspheres was unchanged. Total vascular resistance increased in the lung mainly due to an increase in resistance in arteries and microvessels. Possible mechanisms for increased resistance are compression of small arteries by liquid cuffs and/or occlusion of microvessels by alveolar liquid. (Supported by NIH HL34606 and the American Heart Association.)

## PULMONARY GAS EXCHANGE

5.1

COMPARISON OF $\dot{V}_A/\dot{Q}$ DISTRIBUTION RESOLUTION BY MULTIPLE INERT GAS METHOD (MIGM) WITH A BLOOD GAS METHOD (BGM). R.D. Kaufman*, R.W. Patterson, A.S.J. Lee*. Dept. Anes., UCLA Sch. Med., L.A. CA 90024, Dept. Surg., Morehouse Sch. Med., Atlanta, GA

We determined the dispersion (σ) at which a progressively broadening lognormal $\dot{V}_A/\dot{Q}$ distribution is measurably different from a single compartment (σ=0) plus shunt. A computer model calculates inert gas retentions (R), arterial blood gases (ABG) and mixed venous blood gases (VBG) with inputs of the distribution, λ's, tracheal $Po_2$, base excess, $C(a-\bar{v})o_2$, RQ, Hct, Hgb, and temp. The ABG and R were calculated using distributions of σ=0.1, 0.2, 0.25 log units centered at $\dot{V}_A/\dot{Q}$=.794. The best matching single compartment with shunt was determined for each of these 3 distributions, using both R and ABG as criteria for match. The minimal detectable difference (MDD) in R is assumed to be 5%; in $Pao_2$, 5%; and in $Paco_2$, 2 torr. The R from the best matching single compartment with shunt and from the σ=.25 distribution were indistinguishable (0.8 MDD). The ABG easily distinguished the best matching single compartment with shunt from the lognormal distribution ($\Delta Paco_2$=1.4 MDD, $\Delta Pao_2$=1.8 MDD). While a single compartment and shunt is indistinguishable by MIGM from this lognormal distribution, it is evident that a single compartment will not suffice in the BGM. We found that compartments at $\dot{V}_A/\dot{Q}$=0.45 and 1.4 with equal perfusion and no shunt perfectly matches the ABG of the σ=0.25 distribution at tracheal $Po_2$ of 110, 150, 350 torr.

5.2

**MEASUREMENT OF VENTILATION-PERFUSION INEQUALITY: COMPARISON OF INERT GAS ELIMINATION AND INTRABREATH RESPIRATORY EXCHANGE RATIO.** **J.W. Reed*, H.J.B. Guy*, M.D. Hammond* and G.K. Prisk*. (Spon: J.B. West) Dept. of Medicine, UCSD, La Jolla, CA 92093.**

The slope of the respiratory exchange ratio (R) against expired volume during the course of a slow exhalation may reflect ventilation-perfusion ($\dot{V}_A/\dot{Q}_c$) inequality in the lung (West, J.B. et al., Clin. Sci. 16 529: 1957). This hypothesis has been re-examined in 8 anesthetized intubated dogs by comparing intrabreath R with inert gas (IG) estimates of $\dot{V}_A/\dot{Q}_c$ inhomogeneity. In the supine position the slope of intrabreath R with exhaled volume, Rs, was positively correlated with IG indices. Both Rs and IG demonstrated more inhomogeneity in dogs with larger residual volumes. Following methacholine inhalation the R-expired volume relationship changed materially and Rs increased. The differences between control and post-methacholine values of Rs were significantly correlated with concomitant changes in inert gas indices and $P_aO_2$. During the recovery phase, IG appeared to revert more quickly than Rs, and in 3 dogs had reached pre-challenge values when Rs was still significantly increased. However, the residual effect of methacholine on IG correlated well with the residual effect on $P_aO_2$. This was not the case with Rs. Intrabreath R is a relatively simple, rapid and non-invasive alternative that deserves further consideration. (Supported in part by the Wellcome Research Foundation and the Perkins Memorial Fund).

5.3

REPRODUCIBILITY OF $\dot{V}_A/\dot{Q}$ DISTRIBUTION MEASUREMENTS IN AWAKE MAN AND ANESTHETIZED DOGS. P.D. Wagner. Dept. of Medicine, University of California, San Diego, La Jolla, CA 92093

This analysis of variance examines 3 sets of paired (duplicate) data obtained from 2 different studies: (A) a study of $O_2$ toxicity in 12 anesthetized, ventilated dogs with paired samples taken at 10 points in time for each dog; and (B) a study of 27 resting, asthmatic outpatients using both arterial ($B_1$) and peripheral venous ($B_2$) sampling, the latter weekly for 9 consecutive weeks. For $B_1$, N=69 while for $B_2$ N=217. The 69 values of $B_1$ were obtained simultaneously with an equal sized subset of $B_2$. Both the coefficient of variation (CV) and the absolute % difference (% D) between duplicates in the 2nd moment of the recovered perfusion and ventilation distributions (log $SD_Q$ and log $SD_V$ respectively) were very similar for all 3 groups, and % D did not vary with the magnitude of log SD.

| | | Mean log $SD_Q$ | | | | Mean log $SD_V$ | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | 1 | 2 | CV | % D | 1 | 2 | CV | % D |
| A | 119 | 0.74 | 0.72 | 7.9 | 12.0 | 1.04 | 1.06 | 9.8 | 14.0 |
| $B_1$ | 69 | 0.84 | 0.86 | 8.3 | 12.4 | 0.64 | 0.64 | 7.9 | 11.9 |
| $B_2$ | 217 | 0.73 | 0.75 | 9.2 | 13.7 | 0.60 | 0.61 | 8.1 | 12.2 |

Comparison of $B_1$ and $B_2$ showed peripheral venous sampling ($B_2$) slightly underestimated log SD, on average by 6.8%. Overall, log SD computed as the average of 2 duplicate estimates has a CV of about 6%, both in awake man and in the anesthetized, ventilated dog. Supp. by DRACO AB, Lund, Sweden and HL-17731.

5.4

**DISTRIBUTIONS OF BLOOD FLOW, VENTILATION, TISSUE AND GAS VOLUME IN EDEMATOUS LUNGS.** G. E. Gale*, K. S. Kapitan and P. D. Wagner. Dept. of Medicine, UCSD, La Jolla, CA 92093

Anesthetized dogs were studied, both before and after oleic acid administration, to investigate the distributions of blood flow ($\dot{Q}$), ventilation ($\dot{V}$), tissue volume (T) and gas volume (G) in pulmonary edema. During the first 10 min. of an intravenous infusion of 6 inert gases, their levels were measured in mixed venous and arterial blood (on-line) and expired gas (single-breath collection) by mass spectrometry. Since the rate of approach to steady state elimination is determined by the flow/capacitance ratios in the lungs for each gas, the insoluble gas washins give information about $\dot{V}/G$, while the soluble gas washins reflect $\dot{Q}/T$ relationships. Distributions of $\dot{Q}$, $\dot{V}$, T and G in relation to $\dot{V}/\dot{Q}$, $\dot{Q}/T$ and $\dot{V}/G$ were estimated from the washin data using a linear least-squares ridge regression technique. The value for total T was estimated from the post-mortem lung wet weight. In edema, the mean $\dot{Q}/T$ decreased from 10.6 to 5.3 $min.^{-1}$ whereas mean $\dot{V}/G$ increased from 8.1 to 13.3 $min.^{-1}$ This was mostly due to respective increases in T and decreases in G caused by increases in lung water. Mean $\dot{V}/\dot{Q}$ increased slightly and the range of shunt fraction was .14-.69 for $\dot{Q}$ and .29-.65 for T, with areas of low $\dot{V}/\dot{Q}$ in a few cases. The distribution of shunt generally covered a spectrum of $\dot{Q}/T$ ratios. This method is unique in its ability to estimate distributions of T and G simultaneously with distributions of $\dot{Q}$ and $\dot{V}$. (NIH-HL17731)

5.5

**EFFECTS OF THE BRONCHIAL CIRCULATION ON INERT AND RESPIRATORY GAS EXCHANGE.** K.S. Kapitan. Dept. of Med., UCSD, La Jolla, CA. 92093

**Several pulmonary diseases are accompanied by an impressive expansion of the bronchial circulation and increased bronchial perfusion of the pulmonary capillary bed. During systemic hypoxemia in these conditions, the bronchial circulation has been shown qualitatively to contribute to gas exchange. The quantitative effect of this contribution was studied using a thirty compartment parallel computer model incorporating the bronchial circulation. Several pulmonary and bronchial VA/Q ratio distributions were studied. In general, the quantitative effect of bronchial perfusion on gas exchange was small and depended upon the underlying pulmonary and bronchial VA/Q distributions. Increasing bronchial perfusion lead to decreased retention and increased excretion of middle and low solubility inert gases, corresponding to an effective reduction in perfusion of shunt and low VA/Q compartments. The retention-solubility curve retained its characteristic shape. Distributing bronchial flow preferentially to high VA/Q compartments magnified these effects. For fixed VO2 and VCO2, increasing bronchial perfusion up to 25% of the cardiac output increased PaO2 by 0 to 10 torr, and decreased PaCO2 by 0 to 23 torr, depending upon the distributions of bronchial and pulmonary perfusion. Distributing pulmonary flow to low VA/Q compartments and bronchial flow to high VA/Q compartments maximized these changes. (HL01310)**

5.6

THE CONTRIBUTION OF CARDIOGENIC OSCILLATIONS (CO) TO GAS MIXING DURING CONSTANT FLOW VENTILATION (CFV) Irene J. Cybulsky*, James G. Abel*, Anil S. Menon*, Tomas A. Salerno*, Samuel V. Lichtenstein*, Arthur S. Slutsky. University of Toronto, Toronto, Ont.

CFV is a nonconventional form of ventilation in which normal blood gases can be obtained by insufflating air at a constant flow via two catheters(ID=1.7mm) placed in the main stem bronchi of anesthetized, paralyzed dogs. Although the mechanisms of gas transport during CFV are largely unknown, pulmonary gas flow generated by the beating heart, cardiogenic oscillations, have been postulated to play an important role. To examine this hypothesis, we studied eleven open-chested dogs in a bypass preparation where pulmonary and systemic blood flow were maintained by an extracorporeal pump. Alveolar Ventilation (VA) was calculated using the formula: VA = VCO2*Pb/PaCO2, where VCO2 = CO2 elimination from the lungs (=CFV flow rate*CO2 concentration in the expired gas), and Pb=barometric pressure. Five dogs were placed on right and left heart bypass; following cardiac arrest, VA decreased by 44% ($p<.01$). Another six dogs were placed on left heart bypass only. VA decreased 36% from 3217 to 2051 ml/min ($p<.025$) following ventricular fibrillation. After defibrillation, each dog had an increase in VA, returning to a mean of 81% of the initial bypass beating value. We conclude that cardiogenic oscillations are an important gas transport mechanism during CFV. (Supported in part by MRC(Canada) and PSI Fdn.)

5.7

INFLUENCE OF STRUCTURAL COMPLEXITY ON AXIAL DISPERSION IN THE ACINUS. William J. Federspiel and Jeffrey J. Fredberg. The Biomechanics Institute, Boston, MA 02215.

Existing models of gas-phase species transport in the acinus assume that molecular diffusion dominates axial dispersion, a corollary being that the effective dispersion coefficient in these airways is a constant given by molecular diffusivity, Dmol. This assumption has rested on Taylor's laminar dispersion theory for long straight tubes, which predicts negligible enhanced dispersion when Peclet numbers (Pe) are near unity. We tested the hypothesis that structural complexity of ducts in the acinus promote exaggerated Taylor-like axial dispersion, even when Pe is near unity. A model was developed based on the theory of dispersion in spatially periodic media (Brenner, H. Phil. Trans. R. Soc. A297:81, 1980). Respiratory bronchioles and alveolar ducts were modelled as tubes with outward protrusions (asperities) representing alveoli. The applicable fluid mechanical and convection-diffusion equations were solved numerically, with the complex geometry handled by a boundary-fitted mapping technique. For Pe greater than one the computed axial dispersion coefficients exceeded substantially those attributable to either pure molecular diffusion or Taylor's dispersion for an equivalent long straight tube. Geometrical factors strongly influencing axial dispersion were the asperity volume per unit duct volume and the area through which asperities and central duct communicate. We conclude that under some conditions the mixing of resident and inspired air in the acinus may be substantially underestimated by Dmol. (Supported by HL33009, HL34616, and the National Biomedical Simulations Resource.)

5.8

**CONTRIBUTION OF DIFFUSION TO PHASE III SLOPE FOLLOWING METHACHOLINE EXPOSURE IN DOGS.** G.K. Prisk*, K.S. Kapitan, H.J.B. Guy* and P.D. Wagner. Dept. of Medicine, UCSD, La Jolla, CA 92093.

**We infused saline saturated with He and $SF_6$ intravenously into 7 anesthetized, mechanically ventilated dogs. Instantaneous He and $SF_6$ concentrations at the end of the endotracheal tube (Balzers QMG-511 mass spectrometer) were digitized for 85 seconds at tidal volumes greater than 15 ml/kg. Phase III slopes were measured from ensemble averaged expirograms, with the concentrations normalized to mixed expired values. Four dogs were exposed to inhaled methacholine (MCH) resulting in an average increase in peak airway pressure of 32%, and the measurements repeated.**

**Prior to MCH, phase III slope for He was 0.38 ± 0.39 (s.d.) ΔF/liter (n=57) and for $SF_6$ was 0.76 ± 0.48 ΔF/liter (n=54). These slopes were significantly different (t-test, $P << 0.001$). After MCH, phase III slope for He rose to 1.58 ± 0.62 ΔF/liter (n=23) and for $SF_6$ rose to 2.18 ± 0.58 ΔF/liter (n=24). These slopes were significantly different ($P < 0.001$).**

**We conclude that while diffusive gas gradients play a role in the generation of phase III slope, their effect is much less than the 6 fold difference that would be predicted on the basis of Graham's law alone. Following MCH, phase III becomes 3 fold steeper with even less difference between He and $SF_6$, suggesting that sequential emptying largely determines alveolar plateau slope. (Supported by HL-17731).**

5.9

COMPUTER MODEL OF CONSTANT FLOW VENTILATION

E.P. Ingenito, R.D. Kamm, J. Watson and A. Slutsky

**A computer model describing gas exchange during constant flow ventilation was developed by applying conservation of mass an turbulence energy to each of three serial zones in a 10 generation Horsefield and Cummings model. The 3 zones include: 1.) a region of convective recirculation immediately downdown of the jet; 2.) a region of turbulent eddy transport (extending approximately from generation 4 to 8); and 3.) a region of molecular and Taylor dispersion in the distal airways. Predictions for simulations with $HeO_2$, air, and $SF_6/O_2$ for Reynolds numbers ranging from 2,000 to 50,0000 were similar to those observed experimentally in that: (1) eucapnia could be achieved with gases with catheter flows in the range of 0.2 to 1.6 l/s, (2) gas exchange was most efficient with $SF_6$ followed by air and then $HeO_2$ and (3) $PaCO_2$ approached a constant volume at higher catheter flows. Local impedance to gas exchange was largest in generations 7-just beyond the turbulent eddy zone 5. Predicted $PaCO_2$ were found to be extremely sensitive to jet catheter position and the depth of jet penetration in the recirculation zone. The model also suggests that cardiogenic oscillations play an important role during CFV primarily by improving axial dispersion of turbulent eddies.**

(Affiliations: Brigham and Women's Hospital, M.I.T., and Mount Sinai Hospital Research Institute, Toronto)

5.10

SIMULATION OF GAS EXCHANGE WITH REVERSIBLE AND IRREVERSIBLE VELOCITY PROFILES IN THE PRESENCE OF BROWNIAN DIFFUSIONAL MOTION.

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Interest in the mechanisms underlying successful gas exchange in HFV has resulted in several new proposals for gas exchange mechanisms. A computer simulation of gas flow has been used to quantitatively examine one recently proposed mechanism - convective exchange resulting from velocity profile differences in the two directions of an oscillating flow. The gas transfer was calculated across a cross-sectional plane of a cylindrical tube due to oscillating convective flow and to random diffusional motion of the gas particles. The quasi-steady velocity profiles were allowed to vary in the axial and radial directions such as to satisfy conservation of mass during the flow. The diffusional motion of gas molecules was modeled by a jump vector at each time step with a random direction and length given by the characteristic diffusion distance $(D\delta t)^{0.5}$. In this simplified system, I found that at a Peclet number (PE) of 0.4, where diffusion dominates over convection, that the gas exchanged is insensitive to whether the gas flow is governed by reversible or irreversible velocity profiles. However, as the PE is increased to 400 an oscillating flow with irreversible profiles increases the gas exchanged by up to five times over the gas exchanged with reversible velocity profiles. I conclude that as PE increases, so does the importance of the velocity profiles for gas exchange. (Supported by NIH Grant HL-08805)

5.11

Optimal transport of gas in high frequency oscillations.

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We measured the gas transport produced in tubes and capillaries of various diameter by oscillations with a frequency f varying between 2 and 40 Hz. The transport $D_{eff}$ was expressed as gas flow per unit concentration gradient, per unit area and per unit length (unit: $cm^2/sec$). In all tubes, $D_{eff}$ was proportional to the square of the linear oscillation amplitude ($\Delta x$). In capillaries (ID= .1 and .2 cm) $D_{eff}$ was proportional to $f^2$; in larger tubes (ID=1.5 cm), $D_{eff}$ was proportional to $\sqrt{f}$; in intermediate sized tubes (ID=.8 cm), $D_{eff}$ was proportional to f. Optimal transport ($D_{eff}/2\ \pi f\Delta^2$) was found when oscillation frequency and tube radius are matched according to $f=.28/a^2$. Applied to the bronchial tree these findings explain some of the divergent results obtained by previous authors and point to the difficulty of assessing a single and optimal frequency to a complex system of bronchial tubes of different diameter. The method used was described previously (Phys. Fluids, 26 1380, 1983).

## BLOOD PRESSURE

6.1

DISTRIBUTION OF BODY FAT AND BLOOD PRESSURE IN CHILDREN AND YOUNG ADULTS: THE BOGALUSA HEART STUDY.

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The relationship between central body fat (CBF; measured by subscapular skinfold), peripheral body fat (PBF; measured by triceps skinfold), and blood pressure (BP) was investigated in 3,784 children and young adults, age 5-24 years, from the biracial community of Bogalusa, LA. After adjustment for height, age, and other covariates, significant relationships were found for both CBF (r=0.19 and 0.14), and PBF (r=0.15 and 0.12) with systolic and 4th phase diastolic BP, respectively ($p< 0.0001$). However, the relationship of PBF to BP, after parcelling out the effect of CBF, was found to be negligible (r= 0.00 and 0.01 for systolic and diastolic BP, respectively). In contrast, the CBF relationship to BP remained even after removal of the PBF effect. For CBF, the partial correlations with systolic BP were highest in young children (r=0.15), dropped slightly during adolescence (r=0.12), and became non-significant in 18- to 24-year-old females, while remaining high in both black and white males (r=0.18 and 0.16, respectively). Mean levels of systolic BP from the lowest to the highest quartile of CBF ranged from 100.4 to 108.9 mmHg. The adult hypertension-CBF relationship, which has been shown by others, appears to exist in childhood and continued efforts at early identification and prevention of obesity in children are warranted.

6.2

AUTORADIOGRAPHIC STUDY OF CELL PROLIFERATION IN LARGE MESENTERIC ARTERIES OF SPONTANEOUSLY HYPERTENSIVE RATS.

H. Yang*, W. Morton*, R.M.K.W. Lee and J.B. Forrest*. Department of Anaesthesia, McMaster University, Hamilton, Ontario, Canada, L8N 3Z5.

Our past data showed that hyperplasia is the cause of increased media mass in large mesenteric arteries in 4 week old prehypertensive spontaneously hypertensive rats (SHR). We also found that, at birth, SHR and normotensive Wistar Kyoto (WKY) rats have similar number of smooth muscle cell layers. This study examined when hyperplasia first occurs. Autoradiographic cell counts were done on perfusion-fixed large mesenteric arteries from age matched SHR and WKY rats. Labelling index is defined as number of labelled cells/sum of labelled and unlabelled cells x 1000. Our results showed that labelling index of medial smooth muscle cells was significantly higher in SHR than WKY at 1 week but not at 2 or 4 weeks. Labelling index of endothelium and adventitia were also not different in the three age groups. We conclude, therefore, that SHR smooth muscle cells proliferate faster than WKY between birth and 2 weeks of age. Because this occurs at prehypertensive stage, smooth muscle cell hyperplasia is likely one of the causes of hypertension in SHR.

(Supported by the Heart and Stroke Foundation of Ontario.)

## 6.3

RELATIONSHIP BETWEEN Na AND K CONTENT AND REACTIVITY OF THE DOG SAPHENOUS VEIN. Viktor Berczi* and Geza Simon, VA Medical Center and Univ. of Minnesota, Minneapolis, MN 55417

In mongrel dogs, there is a wide range of spontaneous variation in the total Na content of saphenous veins, and high venous wall Na content is a predictor of malignant one-kidney, one-wrapped hypertension. We hypothesized that high Na content may be a marker of increased vascular reactivity. The saphenous vein of pentobarbital-anesthetized male dogs (N=23) was perfused in vitro with the dogs' own blood, and its reactivity (% increase of initial resistance) to norepinephrine (NE) ($1x10^{-9}$ to $2x10^{-8}$ mol/min) and acetylcholine (ACh) ($5x10^{-8}$ to $2x10^{-6}$ mol/min) was measured. The contralateral saphenous vein was removed for measurements of total and intracellular (Li exchange method at 4°C) Na and K content (mmol/kg dry wt). Intracellular Na to K ratio ($Na_i/K_i$) was calculated. Reactivity to NE (N=16) was unrelated to endogenous plasma NE concentration (range 56-308 pg/ml, r=0.22), total saphenous vein Na content (r=0.38), $Na_i$ (r=0.25) or $Na_i/K_i$ (n=0.12) but was directly correlated with total K content (r=0.65, p<0.01). Reactivty to ACh (N=16) was directly correlated with total Na content (r=0.51, p<0.05) but unrelated to total K content (r=0.25), $Na_i$ (r=0.10) and $Na_i/K_i$ (r=0.02). The findings suggest that the reactivity of saphenous veins to NE relates to cell number or surface area or both per tissue dry weight (as measured by K content), and reactivity to ACh to total tissue Na content. Total vascular wall Na content may be a marker of reactivity to some but not all agonists.

## 6.4

INDOMETHACIN DOES NOT INCREASE THE PRESSOR RESPONSE OF PREGNANT SHR TO ANGIOTENSIN II OR NOREPINEPHRINE. R.A. Ahokas, S.L. Reynolds*, P.J. Hamlett* and G.D. Anderson*. Univ. of Tenn.-Memphis. Memphis, TN. 38163

In pregnant SHR, blood pressure falls progressively during the last week of gestation reaching normotensive levels by term. There is also a close inverse correlation between the changes in blood pressure and blood vessel vasodilator prostaglandin (PG) production. Therefore, it has been suggested that PGs may participate in the antihypertensive effect of pregnancy by contributing to the decrease in pressor action of vasoconstrictor hormones. To test this hypothesis, we measured the blood pressure responses of conscious, unrestrained term-pregnant and nonpregnant SHR, pretreated with either indomethacin (5 mg/kg) or 0.9% saline, to bolus iv injections of angiotension II (AII, 25-400 ng/kg) or norepinephrine (NE, 50-800 ng/kg). All doses of NE, and the three lowest doses of AII, produced significantly greater increases in blood pressure in the saline pre-treated nonpregnant rats than in the saline pre-treated pregnant rats. There were no significant differences between the two groups in the blood pressure responses to the highest doses of AII. Indomethacin pretreatment did not significantly alter the dose-pressure response curves for either AII or NE in either the pregnant or the nonpregnant rats. Thus, increased PG production does not seem to contribute to the reduction of vascular pressor responsiveness to AII or NE, and may not be involved in the antihypertensive effect of pregnancy in the SHR.

## 6.5

**EFFECT OF DIETARY SODIUM ON PLASMA HORMONES AND LEFT VENTRICULAR (LV) MASS.** **Norman F. Paradise, Daniel L. Ely, Susan N. Robinson*, Sandra L. Lovell*, Erhard Haus*, Claude R. Swayze*, St. Paul-Ramsey Med. Center, St. Paul, MN 55101.**

**WKYs and SHRs were fed .03% low (L), .20% control (C), or 3.15% high (H) $Na^+$ diet from age 11 to 20 wks. Rats were anesthetized, blood taken for plasma hormone RIA, and hearts removed. LV hypertrophy, shown by increased LV wt/body wt ratio (LVW/BW), developed in H-$Na^+$ WKYs and was enhanced in H-$Na^+$ SHRs independent of raised systolic arterial blood pressure (SBP). Neither corticosterone (Cort) nor beta-endorphin (Endorph) were affected by diet or strain. Aldosterone (Aldo) was altered only by L-$Na^+$ intake.**

| Group | n | LVW/BW (mg/g) | SBP (mm Hg) | Aldo (ng/dl) | Cort (ng/ml) | Endorph (pmol/l) |
|---|---|---|---|---|---|---|
| WKY-L | 14 | 2.31 ± .06 | 147 ± 4 | 1180 ± 89** | 284 ± 37 | 29 ± 1 |
| WKY-C | 13 | 2.35 ± .11 | 140 ± 3 | 40 ± 6 | 337 ± 50 | 32 ± 2 |
| WKY-H | 13 | 2.73 ± .06* | 141 ± 2 | 12 ± 1 | 274 ± 43 | 28 ± 2 |
| SHR-L | 12 | 2.56 ± .10 | 189 ± 4 | 1086 ± 99** | 317 ± 47 | 29 ± 2 |
| SHR-C | 12 | 2.64 ± .05 | 189 ± 4 | 22 ± 4 | 231 ± 44 | 31 ± 3 |
| SHR-H | 11 | 3.02 ± .14* | 197 ± 6 | 8 ± 1 | 169 ± 30 | 32 ± 3 |

***p <.05, **p <.001 compared with respective control by ANOVA. Compared with previous studies of younger animals, these data indicate that endocrine function is well-maintained in older WKYs and SHRs fed L-$Na^+$ or H-$Na^+$ diet. Also, similar Cort values suggest that altered $Na^+$ intake is minimally stressful. Lastly, the cause of LV hypertrophy due to H-$Na^+$ intake needs further study. (AHA-supported).**

## 6.6

EFFECT OF APROTININ ON THE ACTIONS OF ATRIAL NATRIURETIC FACTOR IN DOCA HYPERTENSIVE RATS. G.C. Awah*, D.W. Zeigler*, and M.L. Kauker. Univ. of South Dakota, Vermillion, SD 57069.

Aprotinin has been reported to potentiate the diuretic and natriuretic actions of atrial natriuretic factor (ANF) in normotensive rats. In this study the effects of aprotinin pretreatment on the hypotensive and renal actions of ANF in normotensive (N) and DOCA-salt hypertensive (H) rats were examined. Mean arterial pressure (MAP), urine flow ($\dot{V}$) and urinary sodium excretion ($U_{Na}\dot{V}$) were measured. Saline was infused (0.02 ml/min) throughout the experiment. Half of the N and H rats were pretreated with aprotinin (1000 KIU/kg/min). ANF was infused at 0.3 µg/kg/min in all groups. Urine was collected at 10 min intervals and MAP recorded. The initial values before, and the changes during ANF infusion are given:

| | | Normotensive | | Hypertensive | |
|---|---|---|---|---|---|
| | | Control | Aprotinin | Control | Aprotinin |
| MAP (mmHg) | Initial | 127±2 | 127±5 | 153±4 | 148±5 |
| | Δ ANF | -28±1 | -27±2 | -51±5* | -49±4* |
| $\dot{V}$ (µl/min) | Initial | 7.3± 1.0 | 8.3±1.3 | 22.9± 4.6 | 20.5±5.1 |
| | Δ ANF | 55.6±12.8 | 46.7±8.2 | 95.0±16.4* | 47.5±8.8† |
| $U_{Na}\dot{V}$ (µEq/min) | Initial | 0.17±0.05 | 0.89±0.18 | 4.80±1.10 | 5.80±1.80 |
| | Δ ANF | 7.30±2.10 | 11.30±2.60 | 19.20±4.60 | 15.50±5.50 |

*$p$ <0.05 compared to N †$p$ <0.05 compared to H controls

These results indicate that aprotinin did not alter the hypotensive action of ANF in the N or H rats, but reduced the diuretic and natriuretic action of ANF in H but not N rats.

## 6.7

AORTIC BARORECEPTORS AND ATRIAL VOLUME RECEPTORS IN THE RESPONSES OF VASOPRESSIN (IR-AVP) AND ATRIAL NATRIURETIC PEPTIDE (IR-ANP) TO VOLUME EXPANSION IN THE ANAESTHETIZED RABBIT. C.A. COURNEYA, N. WILSON and J.R. LEDSOME. Univ. British Columbia, Vancouver, Canada, V6T 1W5.

We examined the responses of IR-AVP and IR-ANP to steplike volume expansion (VE) of 10 and 20% of the blood volume (BV) in 20 urethane/chloralose anaesthetized rabbits. Measurements of IR-ANP, IR-AVP arterial pressure (AP), right atrial pressure (RAP) and heart rate (HR) were made 10 minutes after each VE. Carotid sinus pressure was held constant at 100 mmHg. VE's were performed before and after bilateral vagotomy (VNX) in intact and aortic barodenervated (ADNX) rabbits. In VNX rabbits with intact aortic baroreceptors, 20% VE decreased IR-AVP (-31.2%), increased IR-ANP (+77.6%), AP (+23.8%), RAP (+68.9%) and did not change HR. In ADNX rabbits 20% VE increased IR-ANP (+103.9%), AP (+17.3%), RAP (+267.2%) and did not change IR-AVP and HR. Section of the vagi did not alter these responses. In the ADNX rabbits VNX increased baseline IR-ANP (63.1 ± 8.9 pg/ml to 133.9 ± 37.6 pg/ml). These data suggest that decreased IR-AVP, in response to VE depends on the presence of intact aortic baroreceptors and not atrial volume receptors. Neither set of receptors appear to be essential for IR-ANP release during VE. The increased baseline IR-ANP following VNX may be due to changes in intrathoracic pressure caused by the altered respiration pattern. Supported by B.C. and Can. Heart Foundation.

## 6.8

**INFLUENCE OF VAGUS NERVE AND ACETYLCHOLINE ON PLASMA IMMUNOREACTIVE ATRIAL NATRIURETIC PEPTIDE (IR-ANP) IN THE ANESTHETIZED RABBIT.** **A.J. Rankin*, N. Wilson* and J.R. Ledsome. University of British Columbia, Vancouver, B.C., CANADA.**

**Acetylcholine has been shown to stimulate the release of atrial natriuretic peptide (ANP) in vitro. To investigate a possible role for acetylcholine in releasing ANP in vivo, we measured IR-ANP and hemodynamic variables during acetylcholine infusions and efferent stimulation of the right vagus nerve in the anesthetized rabbit. Infusions of 40 µg/kg/min acetylcholine in 6 vagotomized rabbits led to a small but statistically insignificant rise in IR-ANP from 48.8±5.5 to 66.3±14.7 pg/mL accompanied by a significant increase in right atrial pressure (RAP) and decrease in heart rate (HR) and systemic blood pressure (BP). Similar changes in IR-ANP, RAP and BP were demonstrated when the right atrium was paced to prevent the bradycardia accompanying the acetylcholine infusion. In 5 rabbits, bilateral cervical vagotomy was performed and the peripheral end of the right vagus nerve stimulated. This resulted in a significant increase in RAP and decreases in HR and BP; there was no change in IR-ANP. Simultaneous pacing of the right atrium resulted in no significant change in any of the variables measured. These results suggest that efferent vagal fibres to the right atrium do not constitute a pathway for the release of IR-ANP.**

**Supported by MRC and B.C. Heart Foundation.**

6.9

EFFECT OF SALT ON BARORECEPTOR SENSITIVITY IN THE PREHYPERTENSIVE DAHL SALT-SENSITIVE RAT. S.A. Whitescarver,* M.L. Tashman,* C.E. Ott, and T.A. Kotchen.* Univ. of Kentucky, Lexington, KY 40536.

Gorden et al. (Hypertension, 1981) have demonstrated a decreased baroreceptor sensitivity in Dahl salt-sensitive (DS) rats. The present study was designed to determine if a high salt diet attenuates this decreased baroreceptor sensitivity prior to the development of hypertension. Chronic tail artery and jugular catheters were inserted into 7-8 week old DS and Dahl salt resistant (DR) rats. Two days after surgery baroreceptor sensitivity in conscious animals was calculated as $\Delta$ heart rate interval/$\Delta$ blood pressure (BP) using bolus doses of Phenylephrine (P) and Sodium Nitroprusside (N). DS rats had a decreased sensitivity (p=.01) to P (slope=0.90±.08 ms/mmHg; n=18) compared to DR (1.46±.12; n=9). Sensitivity to N did not differ between DS (1.06±23) and DR (1.23±.17) rats. DS rats also had an increased BP (120±2 mmHg vs. 105±2). Baroreceptor sensitivity was reevaluated in nine DS rats fed either a normal (n=3) or high salt (7% NaCl; n=6) diet for 6 days (just prior to the onset of hypertension). BP was not different between the groups. Baroreceptor sensitivity to P was unaltered by the high salt diet (1.136±.17 vs. 1.038±.17 pre diet). Thus, DS rats have a decreased baroreceptor sensitivity prior to the development of hypertension and a high salt diet does not alter this sensitivity.

6.10

EFFECT OF CERVICAL VAGOTOMY AND THORACIC SYMPATHECTOMY ON RESPONSES OF THE MONKEY TO HEAD-OUT WATER IMMERSION. T.V. Peterson, B.A. Benjamin*, N.L. Hurst* and J.A. Richardson.* Dept. of Medical Physiology, Texas A&M Univ. College of Medicine, College Station, TX 77843

Cardiopulmonary afferent nerves have been implicated as part of a reflex mechanism causing changes in renal excretion during alterations in absolute or central blood volume. Experiments were performed to determine if total cardiopulmonary denervation (vagal & sympathetic afferent pathways) affects the renal responses of the monkey to head-out water immersion, a maneuver which translocates blood to the thorax and elicits a diuresis and natriuresis. Macaca fascicularis monkeys underwent chronic bilateral thoracic sympathectomy or sham denervation. One to two weeks later, they were anesthetized with pentobarbital sodium and the sympathectomized animals underwent cervical vagotomy. Control renal function did not differ between the two groups. Immersion (90 min. duration) increased central venous and arterial pressures similar amounts in both groups but heart rate increased only in the sham denervated animals. Denervation did not affect the renal excretory responses in that the magnitudes and patterns of the increases in urine flow, absolute and fractional sodium excretion and osmolar and free water clearances were similar in both groups. It is concluded that, in the anesthetized monkey, any neural receptor mechanisms mediating the responses to immersion must lie outside the cardiopulmonary region. (Supported by NIH Grants HL31987 and HL01383 and Texas Heart Grant 85G-027).

## CELL BIOLOGY OF WHITE CELLS AND PLATELETS

7.1

**CELL MEMBRANE GLYCOSYLATION IS NEEDED FOR NATURAL KILLER CELL RESPONSIVENESS.** **Charles M. Siraki*, and Anwar A. Hakim. Dept. of Histology, School of Dentistry, and Dept. of Internal Medicine, Stritch School of Medicine. Loyola University Medical Center. Maywood, Illinois.**

**Interleukin-2 (IL-2) is a soluble lymphokine that is produced by mitogenic stimulation of helper T-cell subpopulation. When exposed to IL-2, Natural Killer (NK) cells from healthy adults significantly increased its cytotoxic activity. Whereas, NK cells from patients with breast cancer did not respond to the lymphokine. The present studies examined two possilities: 1. Malignancy release factor(s) that bind to the NK active receptor, and 2. In malignancy, NK cells lack IL-2 receptor.NK cells of healthy donors and of patients with malignant breast carcinoma were isolated by the Ficoll-Hypaque gradient centrifugation and were cultured in standard RPMI-1640 culture medium in absence and presence of non-toxic levels of tunicamycin (Tn). At various transfers, cellular activities were monitored using both proliferative assay determining $^{3}$H-thymidine uptake, cytotoxic activity quantitating the released $^{51}$Cr- from labeled K-623 cells, and monitoring the response to, and release of IL-2. During proliferation, NK cells from healthy adults responded to exogeneous IL-2, and themselves released IL-2 in response to PHA. If grown in media supplemented with Tn, these NK cells did not respond to neither IL-2 nor to PHA. Therefore, cell membrane glycosylation is needed for NK cell responsiveness.Using Con. A-sephadex columns, the eluted products, glycoproteins were present only in NK from healthy donors and increased in response to IL-2.**

7.2

SHEAR STRESS-DEPENDENT POLYMORPHONUCLEAR LEUKOCYTE ADHESION TO ENDOTHELIAL CELLS IN VITRO. S. Gallik,* S. Usami, K.M. Jan, and S. Chien. Columbia U., College of Physicians and Surgeons, New York, NY, 10032. Confluent monolayers of bovine aortic endothelial cells (BAEC) were placed into a parallel-plate-type flow channel which was mounted on the stage of an inverted microscope, attached to a perfusion system, and maintained at 37°C. A randomly chosen field was recorded using videomicroscopy. Human polymorphonuclear leukocytes (PMNs) were coincubated for 15 min. with the BAEC monolayer under control conditions and in the presence of $10^{-7}$M f-methionyl-leucyl-phenylalanine (fMLP). Following incubation, a series of four one-minute flows were driven through the flow channel to expose the cells to four levels of wall shear stress between 1 and 10 dyn/cm$^2$. The leukoresistance of the BAEC monolayer under control conditions was demonstrated by the fact that only 2% of the PMNs remained attached to the BAEC following exposure to 1 dyn/cm$^2$ wall shear stress; less than 1% remained following exposure to 8 dyn/cm$^2$. In the fMLP treated condition, 30% of the PMNs remained attached to the BAEC monolayer following exposure to 1 dyn/cm$^2$ wall shear stress, 19% remained attached following 2 dyn/cm$^2$, 8% remained attached following 4 dyn/cm$^2$, and 5% remained attached following 8 dyn/cm$^2$ wall shear stress. This quantitatively demonstrates the shear stress-dependent nature of PMN-endothelial adhesion during both unactivated and fMLP-activated conditions and the increase in wall shear stress required to detach fMLP-activated PMNs. Supported by HL16851 and HL07114.

7.3

INHIBITION OF PRODUCTION OF INTERLEUKIN-2 BY LYMPHOID CELL CULTURES DURING RETROVIRUS INFECTION. Mayra Lopez-Cepero*, Steven Specter*, Mauro Bendinelli* and Herman Friedman. University of South Florida College of Medicine, Tampa, FL and University of Pisa, Pisa, Italy.

Murine retroviruses, including Friend Leukemia Virus (FLV), induce severe immunosuppression both in vivo and in vitro which is similar to that caused by human retroviruses in patients with AIDS. The mechanisms responsible for the immunosuppression have not been elucidated yet. Recently we showed that interleukin 1 (IL-1) production and response is not altered during the course of infection. However, interleukin 2 (IL-2) production and lymphoid cell proliferation has been shown to be severely depressed. Our studies reveal that Percoll fractionation of spleen cells from FLV-infected mice identifies the T lymphocytes as the affected target of the inhibition of IL-2 production in vitro. These studies rule out the possiblity that the failure to respond to IL-2 is due to a dilution effect by the presence of tumor cells. Adsorption of IL-2 to tumor cells was also eliminated as a cause for the reduction of measurable IL-2. We have shown also that the ability to respond to exogenous IL-2 is compromised in these animals. This failure to produce and respond to IL-2 may be a major factor causing reduced immune function in FLV infection.

7.4

LECITHIN EFFECTS ON BLOOD PLASMA AND PLATELET PLASMINOGEN ACTIVATOR ACTIVITY LEVELS. E. L. Beard, V. L. Weiss,* and J. O. Humphreys*. Loyola Univ., New Orleans, LA 70118.

In vivo studies - New Zealand strain rabbits maintained on an atherogenic, 2% cholesterol diet with a 10% soybean lecithin supplement, developed increased plasma plasminogen activator activity (PAA) compared to atherogenic control rabbits not given the lecithin supplement. After two months the platelets of the lecithin supplemented rabbits had lower PAA in their intact and homogenized platelets and heightened plasma PAA in comparison to atherogenic diet controls. After seven months on these diets, rabbits fed lecithin had heightened PAA levels in their plasma and in their whole and homogenized platelets as compared to atherogenic dieted control rabbit tissues.

In vitro studies - Human blood platelets incubated with cholesterol or Beta lipoproteins in concentrations resembling normal blood lipid levels, retained PAA in comparison to isotonic sucrose control platelets. Following cholesterol incubation, subsequent incubation with lecithin promoted PAA release from the cholesterol treated platelets. Incubation with B-lipoproteins had similar but less pronounced effects as cholesterol on platelet PAA levels. Platelets incubated in lecithin alone lost PAA, in cholesterol alone retained maximum PAA, and in mixtures of lecithin-cholesterol retained intermediate levels of PAA. Lecithin appears to promote platelet release of PAA.

7.5

EFFECT OF IN VIVO HEMOLYSIS ON PLATELET ACCUMULATION ON DACRON GRAFTS. David R. Gross and Fiona Gardiner-McCord*. Texas A&M University, College Station, TX 77843

This study investigated the effect of low level hemolysis (approximately 1%/hr) on the number of platelets which accumulate on a woven dacron arterial graft. The studies were carried out in pentobarbital anesthetized dogs exposed to both a 'control' (saline) and a 'test' (hemolysate) experiment. The order of test and control was randomized with at least 14 days intervening. Each dog received an infusion of autologous $^{111}$In-labeled platelets 1 1/2 hr before each experiment. A 3 cm segment of woven dacron vascular graft was placed, in series, along a section of carotid artery. Blood was diverted through the graft for 1 hr, after which it was removed. The infusion of either physiological saline or hemolysed erythrocytes was begun 10 min prior to graft insertion and continued at rate of 1 ml/kg/hr until the graft was removed. The radioactive count from the graft was converted to a platelet count using a ratio of well count to platelet count from a pre-infusion blood sample. Wilcoxon's signed-rank test was used to show that more platelets accumulated on the dacron in the presence of the hemolysate infusion than in the presence of the saline infusion. The increase due to hemolysis ranged from 2-96% with a mean of 43.7%±35.9 (standard deviation).

This work was supported, in part, by NIH, NCI #CA33531

7.6

IN VITRO MODIFICATION BY COCAINE OF MITOGEN INDUCED PROLIFERATION OF MOUSE AND HUMAN LYMPHOCYTES. Thomas Klein*, Catherine Newton*, and Herman Friedman. University of South Florida College of Medicine, Tampa, FL.

Cocaine is a psychoactive stimulant with an increasing pattern of abuse. In vivo studies have suggested that the sympathomimetic effects of cocaine result in either enhancement or suppression of immune cell activity. In the present study we tested for the direct effects of cocaine in the relative absence of sympathetic control by examing its influence in vitro on the mitogen driven proliferation of mouse splenocyte and human peripheral blood lymphocyte cultures. Splenocyte cultures retained viability at cocaine concentrations as high as 200 ug/ml but lost viability at higher concentrations. Furthermore, mitogen responsiveness of cocaine treated splenocytes was differentially affected in that the proliferation response to Con A was suppressed, the LPS response was unaffected, and the PHA response was increased. Cultures of human peripheral blood lymphocytes were generally suppressed in proliferation responsiveness to both Con A and PHA. These results suggest that cocaine is relatively nontoxic for cultured mouse and human lymphocytes and that varying the concentration of cocaine in culture results in either enhancement or suppression of mitogen driven lymphocyte proliferation.

7.7

INHIBITION BY MARIJUANA COMPONENTS OF KILLING ACTIVITY BUT NOT TARGET BINDING ACTIVITY OF NATURAL KILLER CELLS AND CYTOTOXIC T LYMPHOCYTES. Yutaka Kawakami*, Thomas Klein*, Catherine Newton* and Herman Friedman. University of South Florida College of Medicine, Tampa, FL.

Studies in this laboratory have shown that the marijuana components delta-9-tetrahydrocannabinol (THC) and the hydroxylated metabolite 11-hydroxy-delta-9-tetrahydrocannabinol (11-hydroxy-THC) inhibit the activity of both cytolytic T lymphocytes (CTL) and natural killer (NK) cells. In the present study, the binding activity of these killer cells to target cells was analyzed by the target binding assay. At concentrations as high as 10 ug/ml, THC and 11-hydroxy-THC inhibited target cell killing but not the binding of NK cells to YAC-1 targets or the binding of alloreactive CTL ($H\text{-}2^k$) to the EL-4 targets ($H\text{-}2^b$). Furthermore, THC and 11-hydroxy THC inhibited NK cell activity without killing effectors as determined by trypan blue dye exclusion. However, the suppression of killing activity by THC of in vitro generated CTL was related to possible lytic effects of the cannabinoid on the effector cells. These results suggest that cannabinoids suppress killer cell function by mechanisms other than disrupting target recognition and binding. Supported by grant DA03646 from NIDA.

7.8

DIFFERENTIAL SUPPRESSIVE EFFECTS OF MARIJUANA COMPONENTS ON LYMPH NODE, SPLEEN AND THYMUS CELL CULTURES OF YOUNG VS ADULT MICE. Susan Pross*, Thomas Klein*, Catherine Newton*, Raymond Widen* and Herman Friedman. University of South Florida College of Medicine, Tampa, FL.

Delta-9-tetrahydrocannabinol (THC) is considered the major physcogenic component of marijuana. Studies in this laboratory have shown that THC has marked immunosuppressive effects on thymus cells, moderate effects on spleen cells and virtually no effect on adult lymph node cells stimulated with the plant mitogens Concanavalin A or Phytohemagglutinin (PHA). In addition, when varying numbers of adult cells were cultured ($8x10^6$ - $1x10^6$ cells/ml), it was always easier to suppress the small cell numbers. In the present study, THC had even greater suppressive effects on cultures of dispersed cells from the lymph node or spleen of 4 week old mice rather than adult mice. This was seen in terms of drug dose response studies as well as by using 7 ug/ml THC on varying cell numbers. For example, whereas adult lymph node cells were resistant to suppression to Con A or PHA proliferation at 7 ug/ml THC, the young lymph node cells were more readily suppressed. Similar differences were found between adult and young spleen cells. In contrast, thymus cells responses from adults and young animals were similar. Thus, the effect of marijuana components on the cells from secondary lymphoid organs in vitro is dependent on the animal's age.

## CELL MEMBRANES AND TRANSPORT

8.1

TRIIODOTHYRONINE AND CORTICOSTERONE ENHANCED NAK-ATPASE ACTIVITY IN PRIMARY CULTURED RAT SUBMANDIBULAR GLAND CELLS. Chu S. Lo, Sam Eng*, Laura E. Klein*, and Chin M. Kim*. Dept. of Physiology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814-4799.

The present studies concern the effect of triiodothyronine ($T_3$) and corticosterone on NaK-ATPase activity in primary cultured rat submandibular gland cells. The cells showed a significant increase of 52% in enzyme activity at 24 h ($p<.05$), 119% at 48 h ($p<.01$), and 119% at 72 h ($p<.025$) after $T_3$ ($10^{-7}$M) addition at 24 h intervals. The temporal changes in NaK-ATPase activity after the addition of corticosterone ($10^{-7}$M) showed an increase of 38%, 63%, 50%, and 50% in enzyme activity at 3 h ($p<.05$), 6 h ($p<.001$), 12 h ($p<.01$) and 24 h ($p<.05$) (2 doses of corticosterone at 12 h intervals), respectively. Hence, the time response of NaK-ATPase activity to corticosterone precedes that to $T_3$. Mg-ATPase activity did not respond to either $T_3$ or corticosterone. We further investigate whether these two hormones might be involved permissively or additively in enhancing NaK-ATPase activity. The results showed that the percent increase in NaK-ATPase activity after both corticosterone and $T_3$ (170%) were added was almost equal to the sum of the per cent increases after adding corticosterone (89%) and $T_3$ (103%) separately. The above data suggests that $T_3$ and corticosterone have a direct effect in regulating NaK-ATPase activity in the primary cultured submandibular gland cells and that these two hormones regulate this enzyme via independent pathways.

8.2

MEMBRANE POTENTIALS IN CULTURED SALIVARY GLAND CELLS OF THE RAT: THE EFFECTS OF TRI-IODOTHYRONINE ($T_3$) AND OUABAIN. H.J. Bryant and C.S. Lo. Dept. of Physiology, Uniformed Services University, Bethesda, MD 20814-4799.

Stimulation of membrane bound (Na+K)-adenosine triphosphate (NaK-ATPase) activity increases active Na extrusion and active K uptake leading to hyperpolarization. NaK-ATPase activity is increased significantly in the transitions from the hypothyroid to the euthyroid and to the hyperthyroid states in a variety of tissues including rat submandibular glands. Exposure of primary cultured rat submandibular gland cells to $T_3$ was shown to enhance NaK-ATPase activity. The present study concerns the effect of $T_3$ on the resting membrane potential in primary cultured rat submandibular gland cells. These cells were dissociated by collagenase and hyaluronidase and cultured in a modified Eagle Medium for 5 days. Membrane potentials were measured with glass microelectrodes with the cells in a modified Krebs-Henseleit solution with and without $T_3$ ($10^{-7}$M) and ouabain ($10^{-3}$M) at intervals from 4 hours to 3 days. Membrane potential was unchanged in Krebs-Henseleit solution for a period of 72 hours. Addition of $T_3$ to the solution produced hyperpolarization within 6 to 12 hours. Addition of ouabain to the $T_3$-containing solution produced a depolarization to the same level as did ouabain when added to the Krebs-Henseleit without $T_3$. These results suggest that the hyperpolarization of these cells induced by $T_3$ can be attributed in part to the activation of NaK-ATPase activity. Supported by USUHS C07691, C07623, and NIH AM28590.

8.3

COMPARISON OF MONOSACCHARIDE TRANSPORT KINETICS IN NORMAL RAT RED CELLS AND PHENYLHYDRAZINE-INDUCED RAT MACRORETICULOCYTES. James M. Norton. Univ. of New England, Biddeford, ME 04005.

To investigate changes in the properties of the glucose transporter during erythrocyte (RBC) maturation, the kinetics of 3-O-methyl-D-glucose (3OMG) transport were studied in RBCs from normal rats and in macroreticulocytes from rats with a phenylhydrazine-induced anemia. Highly significant differences in carrier-substrate affinity (Ks) were noted between normocytes and macroreticulocytes for both zero-trans uptake (17.3 and 11.3 mM, respectively) and steady-state exchange (15.0 and 7.9 mM, respectively) of 3OMG. No significant differences in maximum transport rates for 3OMG (Vmax), expressed as mmol/(L cell water-min) or as pmol/($cm^2$-min), were found in the zero-trans experiments; for steady-state exchange of 3OMG, however, values for Vmax were significantly different for normocytes (2.46 mmol/[L cell water-min] or 126.34 pmol/[$cm^2$-min]) and macroreticulocytes (2.77 mmol/[L cell water-min] or 160.28 pmol/[$cm^2$-min]). The differences in Vmax between normocytes and macroreticulocytes are less than that predicted from the calculated difference in cell surface area (99.5 and 146.8 square microns for normocytes and macroreticulocytes, respectively), suggesting a relative conservation of monosaccharide transport sites during RBC maturation despite a loss of membrane surface.

(supported by AHA/Maine Affiliate, Inc.)

8.4

FURTHER CHARACTERIZATION OF THE OUABAIN-INSENSITIVE SODIUM EFFLUX IN BARNACLE MUSCLE FIBERS WITH 4-β-PHORBOL-12,13-DI-BUTYRATE (PD) AS A PROBE. E. Edward Bittar and K. Ueno*. Dept. of Physiology, Univ. of Wisconsin, Madison, WI 53706.

Studies with barnacle muscle fibers have led to the view that the ouabain-insensitive Na efflux can be divided operationally into four distinct components, three of which are modulated by cAMP-PK, cGMP-PK and CM-$Ca^{2+}$-PK. The possible existence of a fifth component has now been investigated using phorbol dibutyrate (PD) as a probe. The results obtained show that external or internal application of PD causes a sustained or transitory stimulation of the ouabain-insensitive efflux, the minimally effective external concentration being ~ $10^{-8}$M. The response to external DB depends on external $Ca^{2+}$:e.g. prior omission of external $Ca^{2+}$markedly reduces the response to external application of $10^{-5}$ M-PD or prevents the response from occurring. Pre-injection of EGTA reduces the size of the response to PD. Substitution of external $Na^+$ by $Li^+$ leads to a delayed and reduced response. Whereas prior application of $10^{-4}$ M verapamil completely abolishes the response to $10^{-5}$ M-PD, both $10^{-3}$ M-$Cd^{2+}$ and $10^{-2}$ M-$Co^{2+}$ are ineffective. However, an elevation in external Mg from 10mM to 50mM suppresses the response to PD. Prior or post-application of amiloride is without effect. Since PL/$Ca^{2+}$ -PK c is present in barnacle fibers (J.F. Kuo, priv. comm.) and since it is the known internal receptor of phorbol esters, it seems likely that a component of the ouabain-insensitive Na efflux is modulated by kinase c.

8.5

ORIENTATION OF MEMBRANE VESICLES ISOLATED FROM RENAL CORTEX. Mitsutoshi Kato* and K. Kako. University of Ottawa, Ottawa, Ontario, K1H 8M5, Canada

Recently it became possible to isolate the basolateral membrane from tubular cells of the kidney cortex. Membrane vesicles could orient in a right-side-out (RO) or an inside-out(IO) state following the isolation procedure. We determined relative amounts of RO, IO and non-oriented membrane vesicles by several methods. Membrane fractions were prepared from dog and pig kidneys by the procedures of Chauhan & Kalra, and Marin et al. Membrane sidedness was examined by 1) the method using (Na+K+)ATPase assays either with monensin and digitoxigenin or with SDS pretreatment, 2) the method using (Na+K+)ATPase assays in the presence of valinomycin, 3) the method using ouabain binding measured with and without SDS pretreatment, and 4) the method using sialidase with and without Triton X-100. The results of analyses using these four methods indicated that the membranes were composed predominantly of RO vesicles (over 78 %), with various amounts of non-oriented ones. However, by using a recently reported procedure, which is based on the binding of lipophilic digoxin to the membrane, preliminary results suggested that the population of IO vesicles may be greater. In conclusion, our results indicate that the membrane vesicles isolated from renal tubules are of predominantly RO orientation, but the proportion of the RO and IO populations could differ depending on the analytical procedure.

## SPLANCHNIC CIRCULATION

9.1

RESPONSES OF GUT TO ADRENERGIC RECEPTOR BLOCKADE DURING HYPOXIA. S.L. Dodd, C.E. King, R.L. Stork*, and S.M. Cain. University of Alabama at Birmingham, 35294.

We tested whether catecholamine effects on blood flow distribution would significantly affect gut $O_2$ deficit during and excess $O_2$ uptake after an acute bout of severe hypoxia. We measured blood flow and $O_2$ uptake in whole body (WB) and gut segments while anesthetized dogs were ventilated with 9% $O_2$ for 30 min followed by 30 min of normoxic recovery. Three groups of dogs were used: 1) control (C), n=10, 2) alpha blockade (AB), n=8, and 3) beta blockade (BB), n=8. $O_2$ deficit and excess were the accumulated differences from the normoxic $O_2$ uptake for both gut and WB with the WB values corrected for $O_2$ stores changes. Whole body deficit and excess did not differ between groups. Gut deficit during AB was less ($p<0.05$) than and gut excess was greater ($p<0.05$) than C or BB values. There were no significant differences in blood flow between treatments, but the $O_2$ extraction fraction was lower ($p<0.05$) in the AB group than in the C or BB groups (AB=0.54, C=0.75 & BB=0.71). BB had no significant effect on gut blood flow or $O_2$ uptake during or after hypoxia. The lesser deficit with AB may have been related to a lower $O_2$ demand in normoxia but $O_2$ extraction still appeared to be more limited than in either BB or C groups. We suggest that AB interfered with redistribution of blood flow within the gut during hypoxia so that functional shunting resulted.

(Supported by NIH grant #HL 26927.)

9.2

ROLE OF HUMORAL FACTORS AND REDUCED VASCULAR SENSITIVITY TO NOREPINEPHRINE IN THE INTESTINAL HYPEREMIA ASSOCIATED WITH EXPERIMENTAL DIABETES MELLITUS. R.J. Korthuis and M.H. Laughlin. Department of Biomedical Sciences and the Dalton Research Center, University of Missouri, Columbia, MO 65211.

Experimental diabetes mellitus was induced by intraperitoneal injection of streptozotocin (STZ, 65 mg/kg). Intestinal blood flow was increased by 40% while intestinal vascular resistance was reduced by 37% in diabetic rats relative to controls. Cross-perfusion of control intestinal preparations with arterial blood from diabetic rats produced a 38% increase in blood flow. Raising plasma glucagon concentration in control rats to levels reported in diabetic animals decreased intestinal resistance by 23%. Increasing plasma osmolality (sucrose infusion) in control animals to levels measured in diabetic animals (575 mosm/l) produced a similar increase in flow as cross-perfusion. Raising plasma glucose levels to 375 mg% in control rats produced an 8% increase in intestinal flow. Intestinal vascular sensitivity to norepinephrine was assessed by constructing dose-response curves in control and diabetic animals. The mean $ED_{50}$ values and maximal responses to norepinephrine were decreased in diabetic rats relative to controls. The results of these studies indicate that 1) humoral or blood-borne factors, including glucagon, hyperosmolality, and elevated plasma glucose and 2) a reduced vascular sensitivity to norepinephrine may account for the intestinal hyperemia associated with diabetes mellitus.

(Supported by HL-36069).

9.3

THE ROLE OF IRON IN OXIDANT-MEDIATED ISCHEMIC INJURY TO INTESTINAL CAPILLARIES. Hernandez, L.A., M.B. Grisham and D.N. Granger. Depts. Physiology & Biochemistry, Univ. South Alabama, Mobile.

Recent reports in the literature suggest that iron plays an important role in free radical-mediated injury in biological systems. In order to assess the role of iron-catalyzed oxidant production in ischemia-reperfusion injury, we examined the influence of desferoxamine (an iron chelator) and transferrin (iron transporting protein) on the increased intestinal vascular permeability produced by one hour of ischemia and reperfusion. Both agents were administered intravascularly as a constant infusion, beginning five minutes before reperfusion. Capillary osmotic reflection coefficients ($\sigma$) were derived from the relationship between lymph-to-plasma protein concentration ratio and lymph flow in the feline small bowel. Vascular permeability ($1-\sigma$) in control intestinal preparations was 0.08 ± 0.005, however it increased significantly to 0.39 ± 0.04 in preparations subjected to 1 hour of ischemia and 30 minutes of reperfusion. Vascular permeability in the desferoxamine (0.156 ± 0.017) and transferrin (0.16 ± 0.048) treated animals were significantly lower ($p<0.01$) than the untreated group. These findings support the hypothesis that iron plays an important role in the formation of oxidants following reperfusion of the ischemic bowel. (Supported by AM33594)

9.4

BLOOD FLOW SHUNTING AND PERSISTENT LACTATE PRODUCTION FOLLOWS REPERFUSION OF ISCHEMIC CANINE INTESTINE. Yonejiro Nakajima* and Ronald W. Millard. University of Cincinnati College of Medicine, Cincinnati, Ohio 45267

Restoration of blood flow is essential if tissues are to survive ischemia. However, reperfusion may also paradoxically exacerbate tissue trauma occurring during ischemia. To determine mechanisms through which adverse reperfusion actions may occur in intestine, jejunal segments of 10 anesthetized dogs were exposed to arterial occlusions lasting 5-60 min followed by 60 min reperfusion. Before ischemia, segment blood flow was 37±6 ml/min/100g, venous oxygen saturation was 65±3% and no net lactic acid production was observed. Ischemia of 5 min was inconsequential. Early reperfusion times (<10 min) following ischemia of >15 min resulted in increased venous oxygen saturation to 79±4% ($p<.05$) and net lactate production of 21±6 mg% ($p<.05$). Persistent and significant lactate production (18±1 mg%) and reduced blood flow (14±3 ml/min/100g) were seen after 60 min reperfusion in segments ischemia of >45 min. Vascular shunting as evidenced by elevated venous oxygen saturation during early reperfusion appears to contribute to reperfusion injury following intestinal ischemia lasting more than 15 min. (Supported in part by NIH AM 34351).

9.5

INTESTINAL BLOOD FLOW AND OXYGEN CONSUMPTION DURING HYPOVOLEMIC HYPOTENSION IN AWAKE NEWBORN LAMBS. Joseph M. Tuggle*, Errol R. Alden*, P. Gary Pettett*, and J. Timothy O'Neill. Dept of Pediatrics, USUHS, Bethesda, MD 20814.

The capacity of the awake newborn lamb to regulate intestinal blood flow (IBF) and oxygen consumption (IOC) during hypovolemic hypotension (HH) has not been investigated. We induced four sequential levels of HH in six chronically instrumented lambs (5.7 ± 0.3 days old) with a pressurized reservoir connected to a hind-limb artery. Arterial pH and hematocrit were maintained with infusions of sodium bicarbonate and autologous red blood cells. At control (69 ± 4.5 mmHg) and each level of HH (lowest=17 mmHg), systemic arterial and portal venous pressure, blood gases and oxygen contents were measured; intestinal perfusion pressure (IPP) was calculated; IBF's were measured by the radioactive microsphere technique; IOC and percent $0_2$ extraction were calculated. Relationships were examined using simple linear regression. IBF decreased with decreasing IPP (slope=1.80 ml/min/100g/mmHg; $p=0.003$). Intestinal vascular resistance and IOC were independent of IPP. Intestinal $0_2$ extraction increased with decreasing IPP (slope = 0.69 percent/mmHg; $p=0.002$). We conclude that in the awake newborn lamb during HH 1) active IBF regulation is not apparent; 2) there is maintenance of IOC as a result of increasing oxygen extraction. (Supported by USUHS C08631)

9.6

EVALUATION OF THE STARLING-RESISTOR-VASCULAR WATERFALL PHENOMENON IN THE LIVER. W. Wayne Lautt, Dallas J. Legare* and Clive V. Greenway, Hepatorenal Research Unit, Pharmacology and Therapeutics, Medicine, U. of Manitoba, Winnipeg, Manitoba, Canada, R3E OW3.

The Starling-resistor waterfall model predicts that upstream blood pressures are absolutely protected against changes in downstream pressure until some critical pressure is reached and beyond that pressure, further increments in downstream pressure will be fully transmitted upstream. In cats and dogs, hepatic venous sphincters are the main site of resistance to portal blood flow. A catheter proximal to the hepatic sphincters measures lobar venous pressure (LVP). The portal venous pressure (PVP) and LVP were determined during a brief occlusion of the vena cava. 55 ± 2% of the rise in CVP was transmitted to PVP. During norepinephrine (intraportal, 1.25ug/Kg per min) and hepatic nerve stimulation (10Hz) the hepatic venous sphincters constricted and the increased resistance led to lesser transmission of CVP (43 ± 6% and 49 ± 4% respectively). The pressure transmission upstream: a) began with small rises in CVP; b) could quantitatively be predicted by an inverse linear relationship with the magnitude of the resistance across which the transmission occurs; c) becomes greater as the rise in CVP increases. Changes in CVP in the face of high resistance will be weakly transmitted upstream but this is due to reduced proportion of transmission over the entire pressure range and not due to having to overcome a "higher waterfall" pressure.

9.7

IS PERITONEAL OXYGENATION FEASIBLE TO IMPROVE SYSTEMIC HYPOXEMIA? J.G. Abel*, I.J. Cybulsky*, S.V. Lichtenstein*, and T.A. Salerno*.(SPON: Arthur S. Slutsky), University of Toronto, Toronto, Ontario, Canada. M5S 1A8

Recent reports in small mammals have suggested the potential for improving systemic hypoxemia by oxygen transfer across the peritoneal membrane from solutions of oxygenated fluorocarbons, hydrogen peroxide, or gaseous oxygen. Theoretical considerations of cardiovascular and pulmonary hemodynamic responses during hypoxia suggest problems with this approach. We studied changes in portal and central venous blood gases in a swine model of hypoxic hypoxia (H). Following hypoxia 5 pigs (27+/-6 kg) had continuous perfusion of the peritoneal cavity with oxygenated Fluosol-DA 20% (F), and 5 pigs (25+/-3 kg) had instillation of 100% gaseous $0_2$ into the peritoneal cavity at 2 L/min. Results (mean +/- SD, paired t-tests with H control) indicate no significant increases in portal or central venous $pO_2$ during either F or $0_2$. During H+F cardiac output (CO) decreased.

| | CO (L/min) | $pO_2$ (mmHg) | | |
|---|---|---|---|---|
| | | Arterial | Portal venous | Central venous |
| H | 3.8+/-0.4 | 43.8+/-8.6 | 29.0+/-5.5 | 30.4+/-5.5 |
| H+F | 2.5+/-0.8** | 39.8+/-8.9 | 26.9+/-5.1 | 25.8+/-5.1* |
| H | 3.0+/-1.6 | 50.9+/-3.2 | 32.2+/-6.9 | 32.5+/-5.6 |
| H+$0_2$ | 2.4+/-1.1 | 47.5+/-7.0 | 28.3+/-8.9 | 28.7+/-6.4 |

* $p<0.05$, ** $p<0.01$ versus H

These results are compatible with decreased splanchnic blood flow during hypoxemia, and a low ratio of splanchnic blood flow to total cardiac output, which precludes use of the peritoneal cavity as a therapeutic shunt.

9.8

**HEMODYNAMIC CHARACTERIZATION OF THE ISOLATED (DENERVATED), PARABIOTICALLY-PERFUSED RAT SMALL INTESTINE.** J.B. Morris,* U.H. Haglund,* and G.B. Bulkley. Johns Hopkins, Baltimore, MD 21205.

A 15-20cm segment of rat jejunum was excised and perfused via an arterial circuit from the femoral artery of a second ("host") rat. The portal venous effluent was drained into a reservoir and pumped back into the host femoral vein. Under control conditions, arterial perfusion pressure ($P_A$) was 79±2mmHg, while portal venous pressure ($P_V$) was set at zero. Blood flow (Q) (cannulating, pulsed, Doppler flowmeter) was 218±14ml/min/100g and vascular resistance (R) was 0.42±0.04mmHg/ml/min/100g (n=23). Resting arteriovenous oxygen difference ($A-V_{0_2}$) was 2.1±0.4 vol %, with oxygen consumption ($\dot{V}_{0_2}$) at 4.7±.8ml/min/100g (n=7). As expected, these values reflect decreased vascular resistance when compared to similar, but innervated, rat intestinal preparations. This preparation remained hemodynamically stable, with no histological evidence of injury after 3 hours. Stepwise reductions in $P_A$ (from 80 to 25mmHg), produced with a clamp on the arterial circuit, showed no evidence for autoregulation of Q (no significant change in R; autoregulatory gain factor = -0.23±.06, n=7). Nor was there evidence of autoregulatory escape during the ischemic periods. However, due to reciprocal changes in $A-V_{0_2}$, $\dot{V}_{0_2}$ was maintained at ~4ml/min/100g over a wide range of Q. When Q was reduced below 69±4ml/min/100g, the compensatory capability for increasing $A-V_{0_2}$ was exceeded, and $\dot{V}_{0_2}$ fell. This is similar to the innervated intestine. This preparation should provide an excellent model for the study of splanchnic hemodynamics and the mechanisms of ischemia/reperfusion injury in the isolated small intestine.

9.9

**EFFECT OF XANTHINE OXIDASE INACTIVATION ON ISCHEMIC INJURY TO THE SMALL INTESTINE.** Dale A. Parks, Julie L. Henson* and D. Neil Granger. Depts. of Anesthesiology and Physiology, Univ. of AL. at Birmingham, Birmingham, AL 35294 and Dept. of Physiology, Univ. of South AL., Mobile, AL. 36688

Oxygen-derived free radicals (OFR) have been implicated in the pathogenesis of the endothelial and epithelial damage associated with ischemia in the small intestine. Competitive inhibitors suggest that the probable source of OFR in ischemic intestine is xanthine oxidase (XO). It was the purpose of the present study to provide further support for the contention that XO is the enzymatic source of OFR which are responsible for the increased vascular permeability associated with ischemia-reperfusion. Administration of sodium tungstate (0.3 g/kg) for 6 days significantly reduced XO activity 84% from 38.4±4.3 to 6.2±1.5 mU/g tissue. Vascular permeability was assessed in autoperfused feline small intestine using the relationship between lymph flow and lymph-to-plasma total protein concentration ratio at filtration rate independence to estimate the osmotic reflection coefficient (σd). One hour ischemia and reperfusion reduced σd from 0.90±0.01 in non-ischemic small intestine to 0.60±0.01, consistent with a dramatic increase in vascular permeability. The tungsten-treated group demonstrated a significantly smaller increase in vascular permeability (0.20±0.02) following ischemia reperfusion. These studies strongly suggest that XO is the enzymatic source of OFR produced during ischemia-reperfusion and that these OFR are responsible for the permeability changes associated with reperfusion of ischemic small intestine.

## GASTROINTESTINAL SECRETION, DIGESTION AND TRANSPORT

10.1

EFFECT OF PARATHYROID HORMONE (PTH) ON GASTRIN SECRETION AND GASTRIC MUCUS IN THE MOUSE. Niall Buckley*, Bruce Lobaugh and George S. Leight, Jr.* (SPON: L.J. Mandel). Duke Med. Ctr., Durham, NC 27710

The pathophysiology underlying the association of peptic ulcer disease and hyperparathyroidism remains obscure. The effect of PTH on gastrin secretion and gastric mucus synthesis, two potential factors in ulcer formation, is disputed. To examine the influence of chronic PTH "stimulation" on these processes, we infused bovine PTH (0.25 U.S.P. U/hr, s.c.) to 20 C57BL/6J mice for 3 weeks via mini-osmotic pumps. In the PTH-infused group, high levels of hormone (>1000 pmol/L) were maintained for the 3 weeks compared to control values 71 ± 15.7 [S.D.]). Calcium and gastrin concentrations rose from the first day of infusion. Calcium peaked on day 3 (14.5 mg/dl) with a mean of 12.9 ± 1.3 for the first week vs. baseline 9.8 ± 0.3 ($p<0.001$). Gastrin peaked on day 5 (276 pg/ml) with a mean of 235 ± 44 over the first week vs. baseline 111 ± 23 ($p<0.001$). Both then fell, and while calcium remained statistically elevated for the 3 weeks, gastrin normalized by the final week. After day 7, the stomachs of 10 mice from each group were excised and stained for mucus content with periodic acid Schiff (PAS). Absorption cytophotometry demonstrated a significant increase in mucus in the PTH group (Optical Density [OD]= 1.1 ± 0.06) compared to that of controls (OD= 0.9 ±0.10, $p<0.005$). The increase in PAS-positive material seen during the phase of high gastrin and calcium levels may reflect a response to hyperacidity. Our data are consistent with a stimulatory role of PTH on gastrin secretion. Whether the underlying mechanism is direct or represents a consequence of events secondary to PTH administration (e.g. hypercalcemia) remains to be elucidated.

10.2

CARBOXY- AND AMINO-TERMINAL FRAGMENTS OF NEUROTENSIN ARE ELEVATED IN HUMAN PLASMA IN RESPONSE TO ORAL FAT. Edwin J. Draviam,* James R. Upp, Jr.* Perry Orchard,* George H. Greeley,Jr., Courtney M. Townsend,Jr., and James C. Thompson. Dept. Surg., The Univ. of TX Med. Branch, Galveston, TX 77550

Neurotensin (NT) is a gut hormone that stimulates pancreatic exocrine secretion. It is not known whether the C-terminal and N-terminal fragments are co-released along with intact NT. The purpose of this study was to characterize the fragments of NT in the plasma of human volunteers in response to oral ingestion of fat. Methods. Lipomul (corn oil, 1 g/kg) was given orally to 6 healthy volunteers. Blood was collected prior to and at 15, 60 and 90 min after Lipomul ingestion. $NT^{1-13}$ and NT fragments were extracted from plasma through C-18 Sep-Pak cartridges, separated and quantitated using a sensitive high-pressure liquid chromatography-radioimmunoassay procedure. Results. (* = $p<0.05$ vs basal).

Plasma NT and NT Fragments Before and After Lipomul (pg/ml)

| | Basal | 15 min | 30 min | 60 min | 90 min |
|---|---|---|---|---|---|
| $NT^{1-8}$ | 36.9±7.7 | 46.4±7.5 | 87.9±9.9* | 137.8±33.3* | 95.0±5.2* |
| $NT^{1-11}$ | 9.7±2.8 | 15.6±2.9 | 27.3±6.2* | 30.5±6.1* | 32.4±10.8 |
| $NT^{8-13}$ | 92.0±25.6 | 189.5±81.2 | 120.0±41.9 | 89.7±13.2 | 92.8±21.0 |
| $NT^{1-13}$ | 39.7±4.9 | 59.5±13.1 | 61.3±11.1* | 55.3±8.6 | 41.0±3.2 |

Conclusion. Ingestion of oral fat in humans causes elevation of both C-terminal ($NT^{8-13}$) and N-terminal ($NT^{1-8}$, $NT^{1-11}$) fragments of NT along with $NT^{1-13}$. The time course of the elevation of the NT fragments suggests that the fragments are co-released.

10.3

INHIBITION OF PEPSINOGEN SECRETION IN GASTRIC GLANDS BY THE CHOLECYSTOKININ ANTAGONIST, ASPERLICIN. L.H. Tang*, M.M. Miller*, L.J. Steiner* and S.J. Hersey. Emory University, Atlanta, GA 30322.

Rabbit isolated gastric glands were used to investigate the antisecretory activity of asperlicin, a newly discovered, nonpeptide antagonist of cholecystokinin (CCK). Asperlicin was found to inhibit pepsinogen secretion stimulated by CCK-8 (sulfated) or gastrin (HG-I) but not secretion stimulated by carbachol or forskolin. Asperlicin did not inhibit acid secretion stimulated by either gastrin or CCK-8. The inhibition of CCK-8 stimulated pepsinogen secretion was found to be competitive, as judged by Schild plots, with a pA-2 value of 6.2. Tritiated CCK-8 was used to measure peptide receptor sites in intact gastric glands. Asperlicin inhibited 70% of the specific (CCK-8 displaceable) binding. Hill plots of binding inhibition by asperlicin were found to be consistent with a simple competition for a single class of binding sites having an IC-50 = 0.7 uM. The results are interpreted to show that asperlicin is a selective antagonist of CCK-type receptors on the gastric chief cell. (Supported by NIH AM 36548 and AM14752).

10.4

A NEW AND SENSITIVE METHOD TO MEASURE PANCREATIC BLOOD FLOW IN DOGS IN RESPONSE TO GUT PEPTIDES. R. Hosotani*, P. Chowdhury, K. Inoue**, T. Tobe** and P.L. Rayford, Univ. of Arkansas Med. Sciences, Little Rock, AR 72205; **Kyoto Univ., Kyoto, Japan.

This study was conducted in anesthetized dogs to measure pancreatic blood flow (PBF) in response to several gut peptides. PBF was measured by Laser Doppler method, a new and sensitive technique for monitoring capillary perfusion. Methods: A total of 10 dogs was used in the study. Under pentobarbital anesthesia, six dogs were injected I.V. with vasoactive intestinal polypeptide (VIP), cholecystokinin octapeptide (CCK-OP), and Peptide HI (PHI) each at graded doses ranging from 3 to 1200 pmol/Kg. Four other dogs received intravenous injections of bombesin (BBS), gastrin releasing peptide (GRP), neuromedin-C (NMD-C), and neuromedin-B (NMD-B) at graded doses ranging from 1 to 300 pmol/kg. PBF was measured continuously by Laser Doppler Method. Results: VIP, CCK-8 and PHI produced dose-dependent increases in PBF: VIP and CCK were almost equally potent and each was approximately 100 times more potent than PHI. BBS, GRP, NMD-C and NMD-B induced dose-dependent decreases in PBF: BBS was approximately 10 times more potent than NMC and GRP and 100 times more potent than NMD-B in decreasing PBF. Conclusion: 1)Laser Doppler is a useful and sensitive method for studying pancreatic blood flow response to gut peptides in dogs. 2)VIP, CCK-8 and PHI caused vasodilation of pancreatic vasculature whereas the bombesin family of peptides (BBS, GRP, NMD-C and NMD-B) caused vasoconstriction.

## 10.5

INTRACELLULAR pH (pHi) RESPONSE TO SECRETORY STIMULATION IN PANCREATIC ACINI. K. Carter*, P. Rutledge*, M. Steer* and W. Silen . Department of Surgery, Beth Israel Hospital, Harvard Medical School, Harvard Digestive Diseases Center and the Charles A. Dana Laboratories, Boston, MA 02215

Resting pHi in mouse pancreatic acini and the pHi 2 minutes after secretagogue stimulation was measured using the fluorescent dye BCECF: 2'-7'-bis (carboxyethyl)-5(6)-carboxyfluorescein. Stimulation of acini in HEPES buffer (pH=7.40) with either $10^{-5}$M carbachol, $10^{-9}$M cerulein, or $10^{-6}$M Ionomycin caused cytoplasmic alkalinization of 0.13, 0.14, 0.18 pH units respectively. The correlation of amylase secretion (induced by $10^{-5}$M carbachol) and cell alkalinization was evaluated at different external pH (pHo). Results (mean ±SE):

| pHo | pHi Resting | pHi after Carbachol | Net stimulated amylase secretion (%total/30 min) | |
|---|---|---|---|---|
| 6.80 | 6.78±.04 | 6.71±.02 | 7.8±0.3 | |
| 7.10 | 7.13±.06 | 7.19±.03* | 11.5±3.9 | |
| 7.40 | 7.19±.06 | 7.32±.04* | 9.2±0.5 | *p < 0.05 |
| 7.70 | 7.48±.10 | 7.49±.06 | 10.1±4.2 | |

These results suggest that carbachol can stimulate amylase secretion over a wide range of pHo, but that cytoplasmic alkalinization associated with secretory stimulation occurs over a restricted range. Furthermore, these findings indicate that secretagogue induced secretion can occur in the absence of cytoplasmic alkalinization.

## 10.6

EFFECTS OF HISTAMINE AND $H_1$ AND $H_2$ RECEPTOR AGENTS ON THE DISSIPATION OF A PROTON GRADIENT IN GASTRIC MUCOSAL SURFACE CELLS OF RABBITS. Edward J. Olender , Tsutomu Furukawa*, Daniel J. Woods* and David G. Fromm . SUNY Health Science Center at Syracuse, Syracuse,NY 13210.

The isolated gastric mucosal surface cell possesses both $Na^+/H^+$ and $Cl^-/HCO_3^-$ exchange systems. This report presents results on the effect of histamine and several $H_1$ and $H_2$ receptor agents on these systems in acid loaded gastric surface cells. The cells were acid loaded by the $NH_4Cl$ prepulse technique and the spontaneous, $Na^+$ and $HCO_3^-$ induced dissipation of the $H^+$ gradient was followed using the metachromatic dye acridine orange. Histamine ($10^{-2}$-$10^{-5}$M) stimulated $HCO_3^-$-induced dissipation, but had no effect on $Na^+$-induced or spontaneous dissipation. The $H_1$ agonist aminoethylpyridine and the $H_2$ agonist dimaprit were capable of mimicing the effect of histamine $HCO_3^-$-induced dissipation, but only at a higher concentration ($10^{-3}$M). The combination of aminoethylpyridine and dimaprit produced histamine-like effects at $10^{-4}$and $10^{-5}$M. The effects of histamine and the $H_1$ and $H_2$ agonists were blocked by either $H_1$ or $H_2$ antagonists. The results suggest that the effect of histamine on $HCO_3^-$-induced $H^+$ dissipation in gastric surface cells is mediated through a coordinated mechanism involving both $H_1$ and $H_2$ receptor sites.

## 10.7

THE ROLE OF LIPOXYGENASE METABOLITES OF ARACHIDONIC ACID IN EXPERIMENTAL ESOPHAGEAL INJURY. B.E. Stein*, M.A. Carroll*, M.L. Schwartzman* and W.S. Rosenthal, New York Medical College, Valhalla, NY 10595.

We have previously shown that rabbit esophagus metabolizes arachidonic acid primarily via a lipoxygenase (LO) pathway to 12-hydroxyeicosatetraenoic acid and, to a lesser extent, via the cyclooxygenase (CO) pathway to prostaglandins. We investigated the role of these two pathways in mucosal damage by determining the effects of indomethacin (Indo), a CO inhibitor, and BW755C, a combined CO-LO inhibitor, on esophageal damage. In situ rabbit esophagi were luminally perfused as follows: Hour 1 - either normal saline at pH 2.0 (AS) or pepsin (2000 units/ml) dissolved in AS (PS); Hour 2 - AS. One PS group each was pretreated with either Indo (5 mg/kg IV) or BW755C (10 mg/kg IV). The loss or accumulation of $H^+$ and hemoglobin into the period 2 perfusate and gross damage (0-4) were measured.

| Results | AS | PS | Indo | BW755C |
|---|---|---|---|---|
| $H^+$ Flux (µmol) | 0.01 | -0.22[a] | -0.16 | -0.39[b] |
| Hb (mg) | 0.06 | 0.58 | 0.69 | 3.85[c] |
| Damage score | 0.0 | 0.8 | 1.0 | 2.4[b] |

a-p<.05 vs. AS; b-p<.05 vs. PS; c-p<.01 vs. PS; n=5 all groups
Inhibition of LO metabolism with BW755C caused a dramatic worsening of esophageal injury by all measured parameters. These data suggest that, unlike other gastrointestinal tissues, endogenous LO metabolites and not CO metabolites are cytoprotective for esophageal mucosa.

## 10.8

DEVELOPMENT OF GASTRIC HYDROLYSIS OF CASEIN AND LACTOFERRIN IN SUCKLING AND WEANLING RATS. J. Britton* and O. Koldovsky. Univ. of Arizona Hlth. Sciences Ctr., Dept. of Pediatrics, Tucson, Arizona 85724.

To evaluate the development of gastric digestion of individual milk proteins, $^{125}$I-bovine casein and human lactoferrin were incubated at 37 °C with flush fluid obtained from the stomachs of 12 day old suckling and 31 day old weanling rats, followed by measurement of radioactivity in trichloroacetic acid-soluble material. In the suckling, little proteolytic activity could be demonstrated using either protein as substrate over a pH range from 3.2 to 7.4. By contrast, hydrolysis of both proteins in the weanling was maximal at pH 3.2. At this pH the rate of casein degradation in the weanling was twice that of lactoferrin and 50-fold greater than that of casein and lactoferrin in the suckling. Analysis of weanling acid-soluble casein degradation products by chromatography on G-50 Sephadex in the presence of sodium dodecyl sulfate revealed three peaks of radioactivity, comprising 65%, 18%, and 12% of the total product in order of elution. We conclude that developmental differences in gastric proteolytic capacity exist in suckling and weanling rats and that individual proteins may differ with respect to their susceptibility to gastric proteolysis in the developing animal.

## 10.9

**INTESTINAL PHOSPHATE TRANSPORT BY HUMAN BASOLATERAL MEMBRANE VESICLES.** Kazuhiro Kikuchi* & Fayez K. Ghishan. Vanderbilt University, Nashville, TN 37232.

Characteristics and mechanisms of phosphate (Pi) transport across the basolateral membranes (BLM) are not defined. Human jejunal basolateral membrane vesicles (BLMV) were prepared using successive differential centrifugation followed by separation on a Percoll density gradient. The purity of the BLMV were validated by biochemical, morphological and functional criteria. The orientation of BLMV were measured by $^3$H-ouabain binding and 63% of BLMV were inside out. D-glucose uptake in BLMV showed no sodium dependency or "overshoot" phenomena, and calcium uptake in BLMV showed ATP dependency. These findings indicated functional BLMV without brush border membrane contamination. At isotonicity, less than 10% of uptake resulted from binding to the vesicle surface. Pi uptake was $Na^+$ dependent and showed saturation, while the passive component was linear and represented a small component of total uptake. The addition of Gramicidin D to $Na^+$ gradient conditions resulted in significant decrease in Pi uptake while trans-stimulation conditions resulted in significant enhancement of Pi uptake. These findings strongly suggest the presence of a $Na^+$ - $Pi^-$ cotransport system in human jejunal BLM. The addition of ATP under $Na^+$ gradient conditions enhanced the uptake of Pi as compared to $Na^+$ gradient condition alone. Valinomycin induced inside negative membrane potential did not alter Pi uptake when compared to "voltage clamp" conditions. These findings are compatible with the presence of electroneutral $Na^+$ - $Pi^-$ cotransporter in the BLM. This study is the first to extensively validate the use of human cadaveric renal allograft donor intestine for BLMV transport studies.

## 10.10

NA+CL-DEPENDENT GLUTAMATE TRANSPORT BY LOBSTER HEPATOPANCREATIC BRUSH BORDER MEMBRANE VESICLES. G. A. Ahearn and L. P. Clay.* Univ. Hawaii, Honolulu, Hawaii 96822

3H-L-glutamate uptake by lobster (Homarus americanus) hepatopancreatic BBMV was stimulated by a transmembrane NaCl gradient (o > i), but not by identical gradients of KCl, TMA-Cl NaSCN, or NaNO3, suggesting a specific dependence of the amino acid transfer upon both Na and Cl. In the presence of an NaCl gradient (o > i), glutamate uptake was strongly dependent upon bilateral pH, increasing markedly as pH was lowered from 7.0 to 4.0. At pH 5.0, Na+Cl-dependent glutamate uptake was not reduced by the presence of the protonophore, CCCP, whereas Na-dependent 3H-D-glucose uptake at this pH was abolished. At a fixed external [Na] (400 mM), 0.05 mM 3H-L-glutamate influx was a hyperbolic function of external [Cl] (25 to 400 mM). The [Cl] resulting in 1/2 maximal glutamate influx ($K_{Cl}$) was 63.6 mM, and the maximal amino acid entry rate ($J_{max}^{Glu}$) was 2.1 pmol/mg/sec. 3H-L-glutamate influx as a function of external [glutamate] at pH 4.0 and 6.0 in the presence of an inwardly-directed NaCl gradient exhibited both carrier mediated and apparent diffusional transport components. Decreasing pH had no significant effect on glutamate influx $K_t$, but tripled maximal entry rate of the amino acid. 3H-L-glutamate influx was strongly trans-stimulated by vesicles preloaded with L-glutamate and L-aspartate, but was unaffected by internal L-alanine, L-lysine, and L-leucine. Data support a model of Na-Cl-glutamate cotransport by a distinct mechanism used by "acidic" amino acids. Supported by NSF grant No. DCB85-11272.

10.11

DUAL ANTIPORT MECHANISMS FOR NA+ AND CL- TRANSPORT BY EURYHALINE TELEOST INTESTINE. J. N. Howard* and G. A. Ahearn. Univ. Hawaii, Honolulu, Hawaii 96822.

Transport mechanisms for NaCl in intestinal brush border membrane vesicles (BBMV) of seawater-adapted tilapia (Oreochromis mossambicus) were investigated. Cotransport mechanisms of NaCl transport (Na/Cl or Na/K/2Cl) were not disclosed. Inwardly-directed gradients of Cl or KCl did not stimulate 22Na uptake, nor was 22Na uptake significantly affected by furosemide under these conditions. In contrast, antiport mechanisms for both Na and Cl transport were disclosed for this preparation. An outwardly-directed proton gradient ($pH_i = 5.5/pH_o = 7.5$) stimulated the uptake of 22Na above that of the control ($pH_i = pH_o = 7.5$). Exogenous amiloride (1 mM) significantly reduced 22Na uptake in the presence of a H+ gradient. Apparent influxes of 1.0 mM 22Na were (pmol/mg prot./15 sec): control, 104.6 ± 5.9; pH gradient, 190.5 ± 17.2; pH gradient + amiloride, 116.6 ± 3.4. Outwardly-directed gradients of formate and Cl significantly stimulated 20 mM 36Cl influx by these vesicles compared to a similar gradient of gluconate. 36Cl influxes under these conditions were (pmoles/mg prot./sec): gluconate, 78.8 ± 39.0; formate, 204.5 ± 70.8; Cl, 316.5 ± 88.5. These results suggest that transport of Na and Cl by tilapia intestinal brush border membrane occurs by dual antiport processes. Supported by NSF grant no. PCM83-19973.

10.12

**INTESTINAL TRANSPORT OF BIOTIN IN RAT INTESTINE IN VITRO.** Hamid M. Said and Reyadh Redha*. Vanderbilt University School of Medicine, Nashville, TN 37232.

Biotin, a water-soluble vitamin, is essential for normal growth and development. The intestinal transport of biotin is not well defined and was therefore investigated in this study. **Method:** Male Sprague-Dawley rats (180-220g) were used. The intestinal everted sac technique was employed and incubation was performed in Krebs-Ringer phosphate buffer pH 6.5 under continous oxygenation (100% $O_2$) at 37°C. **Results:** Transport of 0.1 µM biotin was linear for 30 min incubation and occurred at a rate of 3.7 pmole/g tissue/min. Transport of biotin was higher in the jejunum than the ileum and was minimum in the colon (85 ± 6, 36 ± 6 and 2.8 ± 0.6 pmole/g tissue/25 min, respectively). In the jejunum, transport of biotin was saturable at low concentrations ($K_t$ = 3.73 µM, $V_{max}$ = 3.11 nmole/g tissue/25 min) but linear at higher concentrations (> 10 µM). The transport of low concentrations of biotin was: a) inhibited by structural analogues, b) $Na^+$-dependent, c) energy-dependent, d) temperature-dependent, and e) proceeded against a concentration gradient in the serosal compartment. No metabolic alteration occurs to the biotin molecule during transport. **Conclusions:** Transport of biotin in rat intestine occurs by a carrier-mediated process at low concentrations and a diffusion process at high concentrations. The results also suggest that although biotin is synthesized by the normal colonic flora, the contribution of this source to the total pool of the vitamin may be limited.

10.13

**Evoked release of tritiated norepinephrine ($^3$H-NE) from rat jejunum by electrical field stimulation. Alisa Suvannapura* and Nigel R. Levens*. (SPON: Ping Lee). West Virginia University, Med. Ctr., Morgantown, WV 26506.**

Sympathetic nerves play a physiologically important role in the control of jejunal absorption. Characteristics of sympathetic nerve function have been extensively documented for many organ systems. In contrast, the functional properties of sympathetic nerves innervating the small intestine are poorly understood. Thus, the purpose of this study was to determine functional properties of jejunal sympathetic nerves in response to electrical field stimulation (EFS). 0.5mm slices of rat proximal jejunum were incubated for 40 min in Krebs buffer containing $^3$H-NE. Following incubation, the tissue slices were mounted in glass chambers between 2 platinum electrodes and superfused with Krebs buffer. Release of label from the tissue was determined in response to EFS. At supramaximal voltage (95V), $^3$H-NE release from rat jejunum is frequency dependent. $^3$H-NE outflow from the tissue had a threshold of 1Hz and maximal release occurred at a frequency of 16Hz. Addition of 10µM cocaine to the superfusate decreased the evoked release of $^3$H-NE by 78%. Tetrodotoxin (TTX) also inhibited the evoked release of $^3$H-NE from rat jejunum. However, maximal inhibition of $^3$H-NE release was attained only after reducing the stimulating voltage to 25V. When superfused with a sodium free buffer, the evoked release of $^3$H-NE was reduced by 73%. Removal of calcium from the superfusate also significantly inhibited $^3$H-NE release in response to nerve stimulation. A similar inhibition of $^3$H-NE release was observed after blockade of calcium channels with cobalt chloride. Tetraethylammonium (TEA) acts to prolong the duration of the action potential. In the present study, TEA enhanced the evoked release of $^3$H-NE by 188 fold at 1Hz. However, in the absence of calcium in the superfusate, TEA lost the ability to facilitate the $^3$H-NE release in response to nerve stimulation. These data suggest that EFS induces $^3$H-NE release mainly from sympathetic nerves. The neural release of $^3$H-NE is dependent upon both calcium and sodium and is blocked by TTX. (Supported by AM 30941).

10.14

Angiotensin II (AII) inhibits tritiated norepinephrine ($^3$H-NE) uptake by rat jejunum: **Nigel R. Levens*** and **Alisa Suvannapura*** (SPON: Ping Lee), West Virginia University, Med. Ctr., Morgantown, WV26506.

AII is believed to stimulate sodum and water absorption from the small intestine by enhancing sympathetic nerve transmission. This study sought to determine whether AII could enhance sympathetic neurotransmission within small intestine by inhibiting norepinephrine uptake. $^3$H-NE uptake into small intestine was studied *in vitro* by incubating 0.5 mm slices of rat proximal jejunum in Krebs buffer containing 10nM $^3$H-NE. $^3$H-NE uptake by rat jejunum is an active process which is temperature and time dependent. The uptake process is linear for at least 10 min and begins to plateau after 60 min. $^3$H-NE uptake at 3°C is attributable solely to accumulation of label within the extracellular compartment. Intracellular $^3$H-NE uptake is dose-dependent and fits Michaelis-Menten kinetics with a Km value of 1.11 x $10^{-6}$M and a Vmax of 10 pmole. $g^{-1}$ .$min^{-1}$. Cocaine (1mM) inhibits the intracellular accumulation of the label by 70%. At a dose of 100µM, normetanephrine, an extraneuronal uptake inhibitor, attenuated intracellular accumulation of the label by 15%. Thus, accumulation within sympathetic nerves constitutes the major form of $^3$H-NE uptake into rat jejunum. Previous studies have shown that pretreatment of animals with 6-hydroxydopamine (6-OHDA) completely inhibits $^3$H-NE uptake into rat colon (Am. J. Physiol. 214:G137 - G142, 1981). Using a similar treatment regime, 6-OHDA pre-treatment inhibited intracellular $^3$H-NE uptake in rat jejunum by 60%. Cocaine (1mM) significantly attenuated jejunal $^3$H-NE accumulation in 6-OHDA treated animals. Thus, sympathetic nerves in rat jejunum are more resistant to the effects of 6-OHDA than in rat colon. AII inhibits intracellular $^3$H-NE uptake in a dose-dependent manner. At a dose of 1mM, AII inhibited intracellular $^3$H-NE accumulation by 60%. Cocaine (1mM) failed to potentiate the inhibition of $^3$H-NE uptake produced by AII. Thus, AII prevents $^3$H-NE accumulation within rat jejunum by inhibiting neuronal uptake (Supported by AM 30941).

10.15

VALIDATION OF RELATIVE VISCOSITY (RV) MEASUREMENTS OF CANINE HEPATIC BILE (HB). D.D. Wilson* and H.S. Lowensohn. WRAIR, WRAMC, Washington, DC 20307-5100

We modified the ASTM petroleum industry viscometric method based upon the Cannon-Manning (CM) method (Anal Chem 32:355-358, 1960) by using a flow time of 100s, a within run variation of ≤ ± 0.3%, and a viscometer (V) bile temperature equilibration time of 2 min. Eight anesthetized dogs, used under the 1985 Guide, provided 2-6 ml/hr of HB with IV infusion of 6 µmol/min of Na taurocholate over an 8 hour period. Within 10 min of HB collection, we obtained a 0.2-0.4 ml bile sample for immediate kinematic viscosity determination in triplicate. We tested CM Semi-Micro V sizes 50, 75 and 100 with distilled water (the RV standard) and HB and found that size 75 provided optimal reproducibility with minimal range variation for HB. Chromic acid cleaning of a V after each HB test and subsequent standardization within its previously established flow times is critical. Using V size 75, we ran each HB sample in triplicate accepting all results that were ≤ ± 0.3% of the mean, leading to a rejection rate of 13%. The HB RV for 7 dogs ranged from 1.10-1.47 with a mean of 1.22 ± .09 (SD) and CV = 7.5%, representing a normal profile. Viscosity from HB samples within each normal dog had a variation from 0.6-6.5%. The 8th dog's RV began at 1.85 and steadily rose to 3.30 with marked sample variation suggesting abnormal bile. We validated a method for differentiating abnormal from normal HB viscosity.

12.1

EFFECT OF HEMOLYSIS ON REFLECTION COEFFICIENT DETERMINED FROM ENDOGENOUS BLOOD INDICATORS. Michael B. Maron, Charles F. Pilati*, and Kay C. Maender*, Dept. of Physiology, NE Ohio Universities College of Medicine, Rootstown, OH., 44272.

The osmotic reflection coefficient ($\sigma$) can be estimated from the increases in Hct and plasma protein concentration (Prot) that result when fluid filtration occurs in an isolated perfused organ (Am J Physiol 247:H1, 1984). We determined what effect perfusion pump-induced hemolysis has on the value of $\sigma$ determined with this technique in both the isolated canine left lower lung lobe (LLL) and forelimb by comparing values obtained before and after correction for hemolysis. Hemolysis was corrected by using the slopes of the relationships between Hct & plasma hemoglobin concentration (Hb) and Prot & Hb to correct Hct and Prot to a state of zero hemolysis. These relationships were determined by pumping blood through a perfusion system to produce hemolysis. Results:

| Organ | N | Venous Press | Uncorrec $\sigma$ | Correc $\sigma$ |
|---|---|---|---|---|
| LLL | 7 | 12 torr | 1.19 ± 0.14 | 0.77 ± 0.03 |
| LLL | 6 | 19 torr | 0.90 ± 0.02 | 0.77 ± 0.03 |
| Forelimb | 5 | 21 torr | 0.99 ± 0.03 | 0.85 ± 0.01 |

In 5 additional forelimbs, we cannulated a cephalic lymphatic and determined $\sigma$ using the technique of Granger and Taylor (Am J Physiol 238:H457, 1980) and obtained an average $\sigma$ of 0.88 ± 0.01. We conclude that hemolysis results in overestimations of $\sigma$ which, when corrected, yield similar results to those obtained from lymph analysis for the forelimb and from published lymph values for the LLL. (HL31070)

12.2

SITE OF ALVEOLAR FLOODING IN HIGH PRESSURE PULMONARY EDEMA. Robert L. Conhaim and Abigail Eaton.* CVRI and Dept. of Physiology, Univ. of California, San Francisco, CA 94143

To locate the site of liquid leakage into the airspace in high pressure pulmonary edema, we raised vascular pressure with albumin solution to 15-25 $cmH_2O$ (Palv=5 $cmH_2O$) in 6 isolated, blood-free dog lower lung lobes. After the interstitium was full (120% lobe weight gain), we replaced the vascular albumin with fluorescent (Evans blue) albumin, allowed the weight gain to continue for 90 seconds, then froze the lobes in liquid nitrogen. This fixed fluorescence in the leakage path from the circulation into the airspace. In 300 random 200 um diameter fluorescent fields (30 sections), alveoli were the only fluorescence-filled airspaces, in groups that averaged (means.d.) 4.2±1.3 alveoli in diameter (n=16). Though air-filled, 60% of alveolar ducts (n=243) and 56% of respiratory bronchioles (n=52) were contiguous with fluorescence-filled alveoli. Did liquid enter the airspace at the bronchiolar level then flow peripherally? To test this we inflated 2 lobes to 25% volume with fluorescent albumin then to 100% volume with air. Alveoli were fluorescence-filled. Airways though air-filled had fluorescence lined brush borders. These were not present in the 6 original lobes. In high pressure pulmonary edema we conclude that liquid enters the airspace at the alveolar level, though we cannot rule out entry across squamous cell-lined respiratory bronchioles or alveolar ducts. Supported by Council for Tobacco Research grant No. 1595.

12.3

MECHANICS OF ALBUMIN REABSORPTION FROM THE PLEURAL SPACE IN DOGS. M. Miniati*, D. Martin*, J.C. Parker, M. Pistolesi*, J.T. Cartledge* and A.E. Taylor. Dept Physiol., Univ. of South Alabama, Mobile, AL, and CNR Institute of Clinical Physiol., 56100, Pisa, Italy.

We have previously shown that a bolus of labeled albumin, injected into the pleural space of dogs, is completely recovered in the circulation by 24 hrs. The label recovery showed an initial delay suggesting a lymphatic clearance. To verify this hypothesis, the pleural reabsorption of $^{131}$I-albumin was measured in dogs whose right lymphatic ducts (RD, n=12) or thoracic ducts (TD, n-4) had been ligated prior to the intrapleural injection. Blood samples were collected up to 6 hours after injection; the $^{131}$I-albumin plasma dilution curve was compared with that obtained in dogs with intact lymphatics (n=12). To ascertain a possible direct exchange of albumin between pleural and blood, isolated perfused dog lungs (n=3) were bathed in a 1% albumin solution containing $^{131}$I-albumin; the label appearance in the perfusate was monitored for 3 hrs. The RD ligation significantly reduced the plasma appearance of albumin, the concentration being 10 times lower than in the control group at 6 hrs. The TD ligation reduced the recovery of albumin in plasma, though to a lesser extent than the RD ligation. No albumin was recovered in the perfusate of isolated lungs. These data prove that albumin reabsorption from the dog's pleural space is via lymphatics.

12.4

PLEURAL EFFUSIONS IN VOLUME OVERLOAD PULMONARY EDEMA. C Broaddus*, JP Wiener-Kronish, EH Jerome*, N Matsumoto*, K Miyamoto* and NC Staub. Cardiovascular Research Institute and Dept of Physiol, University of California, San Francisco, CA.

In oleic acid injury, high protein edema liquid entered the pleural space (FED PROC 43:1033, 1984). To measure pleural effusions after high pressure lung edema, we infused 20% body weight of lactated Ringer's solution into five anesthetized, ventilated sheep (30-40 kg) during one hour. We waited one hour more, then exsanguinated the sheep, aspirated all available pleural liquid, and removed the lungs for measurement of extravascular lung water. The data (mean ± SD) are summarized in the table with our normal values. (* p<.05).

| Sheep | No. | Volume (ml) | Protein (g/dl) | Protein Ratio (pleural/plasma) |
|---|---|---|---|---|
| Normal | 21 | 3.5± 3.0 | 1.0±.5 | .16±.08 |
| Overload | 5 | 55.2±28.2* | 2.0±.6* | .46±.21* |

Because the pleural to plasma protein concentration ratio increased, the pleural liquid most likely came from the lung, not from pleural systemic vessels. The pleural liquid volume was approximately equal to the excess lung water. Leakage of pulmonary edema liquid into the pleural space is an important route of edema clearance. [Supported in part by NRSA HL07271 and HL19155 (Pulm Vasc SCOR)].

12.5

PULMONARY MICROVASCULAR PERMEABILITY AND EDEMA "SAFETY FACTOR" AFTER SALINE LAVAGE. B. Nibler,* M.I. Townsley, P. Coker,* and J.C. Parker. Department of Physiology, University of South Alabama, Mobile, AL 36688

The effects of 4 sequential saline lung lavages (L1-L4) using 1.6ml/g wet wt on capillary filtration coefficient (Kfc; ml/min/cmH2O/100g), vascular resistance (RT; cmH2O/ml/min/100g), vascular compliance (Cvas; ml/cmH2O/100g), lung compliance (CL; ml/cmH2O/100g), and critical capillary pressure for exhaustion of interstitial safety factors against edema (Pcrit; cmH2O) was determined in isolated autologous blood perfused lungs of mongrel dogs. Pcrit and Kfc(slope) were determined using the slope and intercept of a plot of the rates of lung weight gain after 3 sequential increases in microvascular pressure. Kfc was also determined by zero time extrapolation of a single weight gain transient.

| | CL | Pcrit | Kfc(slope) | Pci | RT | Cvas |
|---|---|---|---|---|---|---|
| Con | 4.8±.8 | 13.5±1.3 | .078±.009 | 11.3±.6 | .015±.002 | 2.98±.28 |
| L4 | 3.7±.7† | 9.0±1.0† | .174±.044† | 10.0±.4† | .017±.002 | 3.13±.48 |

†p<0.05; means ± SEM.

These data indicate a decreased CL after lavage presumably due to surfactant depletion. Pcrit approached Pci and Kfc (slope) was increased after lavage. This suggests an increased microvascular permeability and/or a reduced ability of the Starling safety factors (lymph flow, interstitial pressure, and oncotic buffering) to oppose transcapillary filtration. (Supported by NIH HL 24571.)

12.6

THE EFFECTS OF HIGH ALVEOLAR SURFACE TENSION ON ALVEOLAR EPITHELIAL PERMEABILITY. G.F. Nieman, C.E. Bredenberg, C. Ritter-Hencirik*, Z. Grossman*, and W.R. Clark*. Depts. of Surgery and Nuclear Medicine, SUNY Health Science Center, Syracuse, NY 13210.

We have shown that high alveolar surface tension (HST) results in pulmonary edema without an elevation in capillary hydrostatic pressure or vascular endothelial permeability. In this study we assess the effects of HST on alveolar endothelial permeability by analyzing the clearance of inhaled Tc-99m DTPA aerosol. Surfactant was displaced by inhalation of the aerosolized detergent diocytl sodium sulfosuccinate (OT) (15 mg/Kg) dissolved as a 1% solution in a vehicle of equal volumes of ethanol and saline. Anesthetized dogs were separated into three groups: Control (GpI) received Tc-99m DTPA aerosol only; HST (GpII) were subjected to OT inhalation; and HST Control (GP III) which received an aerosol of the vehicle without the OT. Inhalation of Tc-99m DTPA began as soon as the OT (GpII) or Vehicle (GpIII) aerosol had been delivered. Blood gases and peak airway pressures (Paw) were recorded and permeability measured as the clearance ($T_{½}$) of Tc-99m DTPA over time. No change was seen in arterial blood gases or Paw from baseline values in GpI or GpIII and $T_{½}$ was 35.4±4.3 and 29.5±2.6 minutes respectively. OT inhalation (GpII) resulted in a marked fall in $PaO_2$ (95±5-39±4 mmHg) and increase in Paw (5±0.3-11±4 mmHg) and $T_{½}$ (9.5±0.5 min). These data suggest that high alveolar surface tension increases alveolar endothelial permeability.

12.7

**COMPUTED FRACTION OF TOTAL LUNG LYMPH WHICH PASSES THROUGH THE CAUDAL MEDIASTINAL LYMPH NODE OF SHEEP.** R. J. Roselli, N. A. Pou* and R. E. Parker. Vanderbilt University, Nashville TN 37235.

We estimated the fraction of total lung lymph which flows through the caudal mediastinal lymph node (CMLN) of three sheep by comparing the node wash-in volume for I-125 albumin with the post-mortem lung albumin equilibrium volume. The wash-in volume was determined by injecting 15 microcuries of I-125 human serum albumin into the plasma and applying a model of unsteady-state protein transport (Roselli et. al., J. Appl. Physiol. 56: 1389-1402, 1984), with interstitial fluid volume held constant, to the concentration of labeled protein collected from the CMLN. Wash-in volume is inversely proportional to the ratio of lymph flow and the time constant associated with the appearance of albumin in the lymph. The proportionality factor depends on the nature of the transvascular barrier and the pressure difference across the microvascular barrier. We used the multiple pore model of Harris and Roselli (J. Appl. Physiol. 50: 1-14, 1981) to characterize this barrier. CMLN lymph fraction computed with this method averaged 0.72 of total lung lymph flow, and ranged from 0.51 to 0.89.

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12.8

EFFECT OF HEMATOCRIT ON LUNG MICROVASCULAR FILTRATION RATE. M Onizuka*, T Tanita* and NC Staub. Cardiovasc Res Inst and Dept of Physiol, Univ of Calif, San Francisco, CA 94143.

Julien (FED PROC 44:1904, 1985) found that increasing hematocrit reduced the rate of weight gain in perfused lung lobes of anesthetized dogs. To study this effect in detail, we measured the combined rates of arterial and venous filtration (lobe weight gain) under zone I conditions (Pvasc = -5 relative to Palv = 25 cmH2O) in isolated, plasma or blood-perfused dog lung lobes. We obtained a peculiar dichotomy of results. If the initial filtration rate using plasma was <.5 g/(min x 100 g), switching to whole blood (Hct = 35%) did not affect filtration rate. But, if the initial filtration rate was >.5, switching to whole blood caused a large decrease in filtration rate. This result was completely reversed by switching back to plasma. The data (read down) are summarized in the table [mean ± 1 SD (No.)].

| | Filtration Rate [g/(min x 100g)] | |
|---|---|---|
| Plasma | 0.25 ±.13(10) | 1.59 ±1.25(10) |
| Blood | 0.31 ±.17 | 0.56 ±0.47 |

In 6 other lobes we compared filtration in zone I (as above) and in zone III (Pvasc = +10 relative to Palv = 10 cmH2O) static conditions. The effect was the same, that is, whole blood lowered filtration rate by 50%, when the initial plasma filtration rate was high. We hypothesize that red blood cells block large leaks that develop in extravascular vessels of isolated lung lobes. [Supported in part by HL36024 and HL25816 (Program Project)].

12.9

FLUID RESISTANCE OF PERIVASCULAR INTERSTITIUM MEASURED DIRECTLY IN ISOLATED RABBIT LUNG. S.J. Lai-Fook, M.R. Kaplowitz* and R.L. Conhaim, Dept. Physiol., CVRI, San Francisco General Hospital, University of California, San Francisco, CA 94143.

Although the interstitial pressure and compliance of the perivascular interstitium have been measured, its intrinsic fluid resistance is not known. We inflated degassed isolated lungs with silicon rubber through the airway and vessels at 15 $cmH_2O$ pressure. After 2 h setting time, we sliced the lung into 1 cm thick slabs. We bonded liquid (3% albumin) reservoirs to the two ends of the perivascular interstitium surrounding a major vein (2.7 mm dia) and applied 5 $cmH_2O$ pressure ($\Delta P$) across the reservoirs. We measured the flow rate (Q) through the interstitium at various mean pressures (Pm). Table summarizes results (n=5, mean + SD):

| Pm ($cmH_2O$) | -2.5 | 2.5 | 10 | 20 |
|---|---|---|---|---|
| $Q/\Delta P$ | .0023 | .0073 | .0134 | .029 |
| ($ml.\ h^{-1}.\ cmH_2O^{-1}$) | +.0026 | +.004 | +.006 | +.008 |

Interstitial conductance ($\overline{Q/\Delta P}$) was proportional to Pm with a zero intercept at -6 $cmH_2O$. We assumed that the interstitium is a porous material with a constant viscosity ($\mu$)-to-permeability (K) ratio, and that flow occurred through an annulus which expanded as pressure was applied to elastic walls. Interstitial thickness averaged 0.031 mm and $\mu/K$ averaged .55±.3 (SD) $cmH_2O.\ h.\ cm^{-2}$, 2 orders of magnitude lower than values cited for the subcutaneous interstitium. (Supported by Program Project HL - 25816 from NHLBI).

12.10

FIBRONECTIN FRAGMENTS IN PULMONARY LYMPH WITH INCREASED LUNG VASCULAR PERMEABILITY DURING INTRAVASCULAR COAGULATION. I. Daudi*, T.M. Saba, P. Vincent*, E. Lewis, and M. Lewis. Dept. Physiol., Albany Med. Col., Albany, NY 12208.

We tested the concept that fragmentation of tissue fibronectin may occur with altered lung vascular integrity during intravascular coagulation. Intravascular coagulation was induced by i.v. infusion of thrombin (80 U/kg for 30 min) in sheep (n=4) with chronic lung lymph fistulas. Lung lymph was analyzed for fibronectin fragments using Western blot analysis. Plasma and lymph immunoreactive fibronectin was assayed by electroimmunoassay. Fibronectin fragments were not seen in lung lymph after surgical preparation of the fistula. In contrast, low molecular weight fibronectin fragments appeared by 1.5 hrs post-thrombin; increased in amount between 3-4 hrs; and disappeared by 5-6 hrs. Following thrombin infusion, there was a 500-800% increase in pulmonary lymph flow ($Q_L$) in association with a decline in lymph-to-plasma total protein conc. ratio (L/P). Transvascular protein clearance ($Q_L$ x L/P) increased approximately 300%. Plasma fibronectin declined and acute peripheral leukopenia developed after thrombin infusion in association with the presence of fibronectin fragments in post-nodal lymph. Thus, fragmentation of lung fibronectin, perhaps by proteases released from marginated leukocytes, may alter its adhesive influence on endothelial cell integrity, thereby contributing to increased lung vascular permeability with intravascular coagulation. (HL-32418; GM-21447; T32-GM-07033; T32-HL-07194)

12.11

EXTRAVASCULAR LUNG WATER IN HEMORRHAGIC PANCREATITIS. Cathy A. Burnweit, M.D.* and Jureta W. Horton, Ph.D. Univ. of TX Health Sci. Cntr., Southwest. Med. Sch., Dallas, TX 75235.

This study measured lung water in pancreatitis(HP) to see if pulmonary dysfunction occurs before changes in clinical parameters. HP was induced in 10 dogs by injecting 0.5 ml/kg bile into the pancreatic duct. Pulmonary and systemic blood gases and blood pressures (PAP,MAP), lung water, heart rate, and lung blood flows(LBF) were studied over 5 hrs while cardiac output(CO) and MAP were supported by Ringer's infusion.

| | CONTROL | 5 HOUR |
|---|---|---|
| MAP, mmHg | 88±5 | 92±8 |
| CO, ml/kg/min | 131±7 | 128±9 |
| PAP (sys/dias), mmHg | 15.6±1.8/8.1±1.3 | 22.0±1.2/15.6±1.7* |
| Pulm wedge (PW), mmHg | 5.3±0.6 | 5.6±0.4 |
| LBF, ml/g/min | 1.87±0.45 | 0.86±0.25* |
| PVR, units | 7.5±2.0 | 82.8±23.0* |
| $p_AO_2$, mmHg | 111±8 | 110±10 |
| $ppAO_2$, mmHg | 46±2 | 35±4* |
| Lung $H_2O$, ml/kg | 10.2±0.8 | 18.1±2.8* |
| Lung $H_2O$, % | 78.1±0.3 | 86.4±2.4* |

PVR=pulmonary vascular resistance; $p_AO_2$, $ppAO_2$ =partial pressure $O_2$ in systemic and pulmonary artery. *Denotes p<0.05. Although arterial oxygenation was maintained, increased PAP and PVR likely contributed to increasing lung water. Blood gases do not reflect the pulmonary deterioration in HP. Our data support a mechanism of lung dysfunction independent of the circulatory compromise often accompanying HP.

12.12

EFFECT OF HUMAN PLASMA FIBRONECTIN INFUSION ON LUNG VASCULAR PERMEABILITY DURING BACTEREMIA. L. Cohler*, T. Saba, and E. Lewis. Dept. Physiol., Albany Med. Col., Albany, NY 12208.

Lung vascular injury occurs during sepsis in association with plasma fibronectin (FN) deficiency. Tissue FN between endothelial cells and in basement membranes may influence vascular integrity. Plasma FN modulates reticuloendothelial function and can incorporate into the tissue FN pool. We studied the effect of purified human plasma FN (USV Pharmaceuticals; RHCG) on lung fluid and protein flux during Pseudomonas bacteremia using the chronic sheep lung lymph fistula. FN was given iv bolus (100 mg) 2 hrs prior to bacteria, with an infusion of 100 mg/hr for 4 hrs. Sheep received bacteria ($5x10^8$) i.v. over 1 hr, 2 hrs after start of FN infusion. Controls (n=7) showed an early 308% rise in lung lymph flow ($Q_L$; 0 hr=4.7±1.1 ml/hr; 2 hr=14.4±3.5 ml/ hr) and a decline in lymph/plasma total protein conc. (L/P) ratio (1-2 hrs), followed by a sustained 300-400% elevation in $Q_L$ (3-12 hr) with an increase in L/P ratio. Increased (380-480%) lung protein clearance (LPC=$Q_L$xL/P ratio) normalized by 24 hrs. An early increase in $Q_L$ (240%) and decline in L/P ratio was also seen with human FN therapy (n=4), but the sustained increment in LPC (3-12 hrs) was markedly attenuated. Sheep plasma FN declined 22% by 6 hrs in controls but did not decline with human FN therapy. Thus, infusion of plasma fibronectin attenuates increased lung vascular permeability with post-operative sepsis which may be due to its opsonic and/or adhesive functions. (GM21447;T32GM07033)

12.13

INFLUENCE OF FIBRINOLYSIS INHIBITION ON GLASS BEAD EMBOLIZATION IN CANINE LUNG. B. Twohig,* A.E. Taylor, and M.I. Townsley. Department of Physiology, University of South Alabama, Mobile, AL 36688.

The effects of partial fibrinolysis inhibition on glass bead embolization were studied in isolated blood perfused canine lung lobes (56.8±6.3g, mean±SE). Beads (E, 0.6g/Kg) were infused into the lobe in situ with (n=6) or without (n=8) prior tranexamic acid (TEA, 50mg/Kg bolus followed by 0.83mg/Kg/min until lobe excision). Within 30 min of perfusion isogravimetric pulmonary arterial and venous pressures were 22.1±1.7, and 4.2±0.1 cmH2O in E lungs, respectively, while flow was 536±69 ml/min/100g. TEA did not alter these parameters. There were no significant changes with time in either group. At 120 min, total vascular resistance was not altered by TEA (72.7±31.4 vs 41.2±11.1 cmH2O/l/min/100g) although the ratio of pre- to postcapillary resistance (Ra/Rv) was increased (6.08±1.24 vs 2.88±0.45, $p<0.05$). The effects of TEA on vascular permeability were inconsistent: the filtration coefficient was increased (0.29±0.05 vs 0.18±0.02 ml/min/cmH2O/100g, $p<0.05$) while isogravimetric capillary pressure (7.7±0.8 vs 8.6±0.6 cmH2O) and the osmotic reflection coefficient (0.41±0.03 vs 0.54±0.02) were not significantly decreased after TEA. Though TEA does alter Ra/Rv and thus will influence capillary filtration pressure in vivo, partial inhibition of fibrinolysis does not clearly exacerbate emboli-induced pulmonary vascular injury. (Supported by NIH HL 22549.)

12.14

EFFECTS OF ENDOTOXEMIA ON AN IN SITU SHEEP LUNG LYMPH PREPARATION. R.E. Parker, R.J. Roselli, K.L. Brigham and T.R. Harris. Vanderbilt University, Nashville, Tn. 37235

The effects of endotoxemia on lung fluid balance were studied in 3 in situ sheep lung lymph preparations and the results compared to 2 control in situ preparations; all of which were perfused with an autologous blood/Ringer's Lactate solution. The results indicate that over 4-5 hours of perfusion the control preparations were very stable as evidenced by alveolar hypoxic response; multiple indicator urea PS and extravascular lung water; bloodless wet/dry weight (W/D); constant perfusion pressures, lung lymph flow rate (QL), and lymph/plasma protein concentration ratio (L/P). The 3 endotoxemia preparations had responses similar to unanesthetized sheep preparations in that we observed a typical Phase 1 response (pulmonary arterial hypertension, increased QL, decreased L/P); and a typical Phase 2 response (high QL with protein rich lymph, relatively normal vascular pressures). An increased lung microvascular permeability during Phase 2 was also indicated by multiple indicator urea PS and extravascular lung water; elevated W/D; and increased prostacyclin production (as measured by 6-keto-PGF1a). Our results indicate that the in situ sheep lung lymph preparation may be an ideal model for the study of endotoxemia in which precise control of experimental variables is mandated.
Supported by Grant Nos. HL 19153 and HL 27169.

12.15

LEUKOTRIENE $C_4$-IMMUNOREACTIVE SUBSTANCES ARE NOT INCREASED IN BRONCHOALVEOLAR LAVAGE FLUID FROM ENDOTOXEMIC PIGS. N.C. Olson*, L.N. Fleisher,* R. Dobrowsky*. (SPON:C.E. Stevens). North Carolina State University, Raleigh, NC 27606.

Infusion of endotoxin into anesthetized pigs causes acute respiratory failure (ARF). We hypothesized that peptidoleukotrienes might be important to the pathophysiology of ARF and, if so should be recoverable from bronchoalveolar lavage (BAL) fluid. We used RIA, RP-HPLC and guinea pig ileum bioassay to determine the presence of $LTC_4$- immunoreactive substances in BAL fluid recovered from saline-(n=12) and endotoxin-(n=12) treated pigs. Endotoxin, infused at 5 µg/kg for 1 hr followed by 2 µg/kg/hr for 3.5 hrs, caused pulmonary hypertension, a biphasic increase in pulmonary vascular resistance, hypoxemia, pulmonary edema and increased BAL albumin concentration. After 4.5 hrs, the level of $LTC_4$-immunoreactive substances recovered from BAL fluid was 793 ± 206 pg/ml in control pigs and 956 ± 308 pg/ml in endotoxin-treated pigs. During RP-HPLC, ethanol extracted BAL fluid failed to show an UV absorbance peak (280 nm) that was coincident with authentic standards. Concentrated BAL samples and BAL eluate fractions (collected at a retention time consistent with authentic $LTC_4$) failed to cause a sustained contraction of guinea pig ileum. We conclude that $LTC_4$ is not increased in BAL fluid recovered from endotoxemic pigs and that the peptidoleukotrienes may not be important factors contributing to the pathophysiology of endotoxin induced ARF. Supported by NIH HL32726.

12.16

FLANK LYMPH FLOW IN SHEEP WITH SURFACE BURNS AND/OR SMOKE INHALATION. J. Stothert, Jr., D. Herndon, M. Brown*, L. Traber*, D. Traber. Univ. Tx. Med. Br. & Shriners Brn. Inst., Gal., TX 77550

Sheep (N=29) were divided into 4 groups. GI, a control group; GII, airway inhalation of a standardized smoke preparation; GIII, combination of third degree surface burn and smoke inhalation; GIV, had surface burn alone. These animals were chronically instrumented with a functioning cutaneous lymph. All animals were fully anesthetized during inhalation of smoke and/or creation of the surface burn. Significance was determined by student's t-test between these two periods (*p less than .05.).

| | GI | | GII | | GIII | | GIV | |
|---|---|---|---|---|---|---|---|---|
| Hour | 0 | 48 | 0 | 48 | 0 | 48 | 0 | 48 |
| Extravascular Lung Water (ml) | 404 | 431 | 396 | 608* | 368 | 549* | 285 | 325 |
| Cutaneous Lymph Flow (ml/hr) | 3.0 | 3.1 | 3.2 | 4.8 | 6.9 | 12.3* | 3.7 | 8.7* |
| Cutaneous Lymph/Plasma Protein Ratio | 0.25 | 0.13 | 0.36 | 0.20 | 0.35 | 0.34 | 0.29 | 0.30 |

These data indicate that cutaneous lymph flow increases more with surface burns than smoke inhalation. Comparing these data to previous reports reveals a generalized increase in membrane permeability does not appear to occur after smoke inhalation. This suggests that a localized process in the lung accounts for increased pulmonary protein permeability after smoke inhalation.

12.17

EFFECT OF CIMETIDINE ON PULMONARY OXYGEN TOXICITY IN LAMBS. T.A. Hazinski, K.A. Kennedy*, R. Epps*. Department of Pediatrics, Vanderbilt University Medical School, Nashville, TN.

We recently reported that a single dose of endotoxin reduces pulmonary oxygen toxicity by a mechanism that does not involve the induction of antioxidant enzymes but increases lung glutathione levels (Ped Res 20:473A, 1986). One of endotoxin's many effects is to inhibit cytochrome P450, an enzyme system present in the lung and known to produce oxygen radicals. Therefore, we gave a single dose of another P450 inhibitor, cimetidine (C), to 7 lambs and then placed them in >95% $O_2$. Vascular pressures, gas exchange, lymph flow ($\dot{Q}_L$) and lymph protein clearance (LPC) were measured each day in $O_2$. Variables measured after 72h in $O_2$ are shown below for 5 control lambs and for the C-treated lambs (means only, *indicates $p<.03$):

| | PA | LA | pH | pCO2 | pO2 | $\dot{Q}_L$ (x baseline) | LPC (x baseline) |
|---|---|---|---|---|---|---|---|
| $O_2$ alone | 13 | -1 | 7.22 | 71 | 403 | 3.2 | 3.3 |
| $O_2$+C | 15 | 0 | 7.39* | 44* | 466 | 1.1* | 1.2* |

The C-treated lambs lived longer (136±15h vs 83±11, $p<.02$) and post-mortem lung water was less (4.2±1 vs 6.5±.9, $p<.02$). Antioxidant enzymes were not different in the two groups, but the ratio of reduced-to-oxidized glutathione was 15-fold greater in the C-treated lambs. Lung microsomal P450 activity in C-treated lambs was <30% of that measured in $O_2$ controls. We conclude that cimetidine prolongs survival, maintains gas exchange, delays the increase in microvascular permeability, and reduces lung P450 activity. These data suggest that the pulmonary P450 system may be important in the pathogenesis of pulmonary oxygen toxicity.

12.18

EFFECT OF CATALASE, SUPEROXIDE DISMUTASE, AND DEFEROXAMINE ON PHORBOL MYRISTATE ACETATE (PMA)-INDUCED LUNG INJURY. R.C. Allison, E.M. Hernandez, V.R. Prasad, and A.E. Taylor. Dept of Physiology, University of South Alabama, Mobile, AL 36688

We used isolated dog lung lobes perfused with blood (550 ml) at constant pressure in Zone III to study the pretreatment effect of 3 drugs on PMA-induced lung injury. The effect on vascular permeability, as determined by filtration coefficient (Kf) and isogravimetric capillary pressure (Pci), and on pulmonary vascular resistance (PVR) was observed. Group PMA lungs (n=5) received 50µg PMA as did the other groups; Group CAT lungs (n=5) were pretreated with catalase (400mg) 3 min before PMA; Group SOD lungs (n=6) were pretreated with superoxide dismutase (32-64mg) before PMA; and Group DEF lungs (n=4) were pretreated with deferoxamine (300-500mg). Baseline (BL) values for Kf (g/min/cm$H_2O$/100g lung), Pci (cm$H_2O$), and PVR (cm$H_2O$/L/min/100g lung) are compared to those obtained 1 Hr after PMA:

| | Kf | | Pci | | PVR | |
|---|---|---|---|---|---|---|
| | BL | 1Hr | BL | 1Hr | BL | 1Hr |
| Group PMA | 0.17 | 1.10 | 9.9 | 6.8 | 14.3 | 132.6 |
| Group CAT | 0.21 | 0.40 | 8.5 | 7.2 | 10.9 | 35.4 |
| Group SOD | 0.18 | 0.95 | 9.1 | 8.5 | 8.8 | 22.3 |
| Group DEF | 0.18 | 0.43 | 9.1 | 7.9 | 9.8 | 24.8 |

PMA causes an increase in both vascular permeability and vascular resistance. The increase in permeability appears to be attenuated by catalase and deferoxamine, but not by superoxide dismutase. (Supported by NIH HL 01411.)

12.19

EFFECTS OF PHORBOL MYRISTATE ACETATE (PMA) IN ISOLATED RAT LUNGS. M.L. Perry,* M.I. Townsley, and A.E. Taylor. Univ. of South Alabama, Mobile, AL 36688

Isolated rat lungs (1.8-3.3g) perfused with whole blood (n=6) were treated with intratracheal PMA (20µg). The capillary filtration coefficient (Kf,c, ml/min/cmH2O/100g) and isogravimetric capillary pressure (Pc,i, cmH2O) were measured during a control period and after PMA. Pulmonary arterial (Pa) and venous pressures were initially 16.8±.9 and 3.3±.5 cmH2O at a blood flow of .338±.029 l/min/100g (mean±SE). Results are given in the following table where Ra and Rv are pre- and postcapillary resistances (cmH2O/l/min/100g):

| | Pc,i | Kf,c | Ra | Rv |
|---|---|---|---|---|
| Control | 8.2±.5 | .18±.05 | 27±4 | 15±2 |
| PMA | 6.3±1.0 | .75±.25 | 1005±434 | 248±70 |

2.3h after PMA, Kf,c, Ra and Rv were markedly increased ($p<.05$). Pc,i did not decrease significantly after PMA, possibly due to concomitant increases in tissue hydrostatic pressure. Blood flow was decreased to .044±.014 l/min/100g to maintain an isogravimetric state. However, if blood flow had remained constant, as in the intact animal, prevailing Pc and Pa would be 84 and 424 cmH2O, respectively. Thus, while the edema resulting from PMA is due in part to increased permeability, we predict that the increase in hydrostatic pressure would also contribute significantly to edema formation in intact animals and possibly stretch pores in the lung's microcirculation exposed to such excessive pressures.

12.20

AMPHOTERICIN CAUSES NEUTROPHIL INDEPENDENT INJURY IN RAT LUNGS. T.J. McDonnell* and N.F. Voelkel. CVP Research Lab., UCHSC, and Webb Waring Lung Inst., Denver, CO 80262

Amphotericin B (AMPH) has been associated with lung injury clinically (N.E.J.M. 1981; 304:1185-1189) but this remains controversial and the role of the neutrophil is unclear. We wondered whether AMPH could produce lung injury experimentally. We injected rats with IV AMPH and used radiolabeled albumin ($^{125}I$) and RBC's ($^{51}Cr$) to estimate extravascular accumulation of albumin. The extravascular lung/blood albumin ratio in control lungs (n=12) was 0.30±0.02 and following AMPH (1 mg/kg; n=9) rose to 2.41±0.58 ($P<0.05$ from control). Seven rats were pretreated with cyclophosphamide to produce neutropenia and following AMPH 0.75 mg/kg had a mean extravascular lung/blood albumin ratio of 2.22±0.98 ($P<0.05$ from control). Thus, neutropenia did not protect against lung injury. In addition, we examined the effects of AMPH on isolated rat lungs perfused with a cell and plasma free physiological salt solution containing ficoll. AMPH 0.5 ug/cc perfusate (n=5) produced vasoconstriction ($\Delta P$ 17.5±1.39 mmHg) and increased the extravascular accumulation of $^{125}I$ albumin. We conclude that AMPH can cause lung vascular injury in rats which appears to be independent of neutrophils.

## NEURAL CONTROL OF CIRCULATION I

13.1

THE EFFECT OF H1-ANTIHISTAMINES ON THE BLOOD PRESSURE AND HEART RATE IN THE "AN-AUTONOMIC" DUCK. L. Beck*, G. Friedrichs*, P. Peterson*, R. S. Pozos*, and L. E. Wittmers Jr.* (Spon: D. Mohrman) Dept. of Physiology, U of Minnesota-Duluth School of Medicine, Duluth MN 55812.

H1-Antihistamines (AH1) were originally reported to block a component of reflexly induced vasodilation in the anesthetized dog by Beck (Pharmacologist, 1958). The observation has since been confirmed in several classes of mammals by a number of investigative groups. In1982 Beck et al.(Fed. Proc.41(No 5) :1682;1982) showed that intraarterial administration of AH1 increased perfusion pressure in a limb perfused at constant flow . Beck et al. (Proc. West Pharmacol. Soc. 14: 63-67, 1971) also reported that sympathetic chain section in the dog increased histamine release. Such observations suggest that in the anesthetized animal, histamine circulates in physiologically vasoactive quantities and that the release is governed at least in part by the amount of adrenergic tone. Because adrenergic tone is elevated in anesthetized animals, we tested the effect of AH1 on the blood pressure (BP) and heart rate (HR) in unanesthetized ducks (local anesthesia only) to see if there is evidence for a greater component of cardiovascular activity in the absence of anesthesia. In addition large doses of guanethidine, propranolol and atropine were previously administered to prevent reflex autonomic adjustments from occurring, which might otherwise cloud interpretation of the response. Following the administration of these drugs, control observations were made, followed by iv administration of tripelennamine, 3 mg/kg, whereupon the observations were repeated. Tripelennamine (AH1) increased resting BP from 138 mmHg to 210 mmHg ($p<0.01$). Surprisingly AH1 also lowered HR from 283 to 218 beats/min ($p<.001$). The considerable rise of BP in this unanesthetized "an-autonomic" preparation implies a physiological regulatory role of histamine on the BP and vascular tone. The highly significant effect of AH1 on HR may suggest H1-type receptors for histamine in the duck heart, or alternatively, that a non-adrenergic, non-cholinergic mechanism is involved in buffer regulation of HR & BP in the duck. Supported in part by Minnesota SEA Grant project RS/5 #196 and ONR #N00014-84-K-0224.

13.2

THE EFFECT OF H1-ANTIHISTIMINES ON DIVING AND EMERSION RESPONSES IN THE "AN-AUTONOMIC" DUCK L.W. Wittmers Jr.,* P. Peterson*, G. Friedrichs*, R. S. Pozos* and L. Beck*. (Spon: D. Mohrman). Dept. of Physiology, U of Minnesota-Duluth School of Medicine, Duluth MN 55812

The results presented in the accompanying abstract indicate that histamine exerts a physiologically significant regulatory role in the maintenance of blood pressure (BP) and vascular tone under basal conditions. The results also implicate histamine directly or indirectly as a physiologically important regulator of heart rate (HR). HR and total peripheral resistance are known to undergo dramatic changes when the dive reflex is elicited in the Mallard duck. We tested the effect of H1-antihistamine (AH1;tripelennamine) on HR and BP during simulated diving for 60 sec (beak immersed in water above the nares) and during emersion. In untreated ducks diving normally induces marked alterations in parasympathetic and sympathetic activity to the heart and blood vessels. To avoid the possibility that the AH1 may induce secondary effects on these adrenergic and cholinergic components of autonomic activity, we rendered ducks essentially "an-autonomic" by chronically treating with guanethidine to deplete adrenergic nerves, and by acutely treating with atropine and propranolol to block cholinergic parasympathetic and circulating (adrenal medullary) beta adrenergic influences on the heart. Pretreatment with guanethidine, atropine and propranolol increased resting predive HR to 155% of control and increased BP to 123% of control. Pretreatment with these drugs nearly eliminated the very large decrease in HR normally seen in untreated ducks during diving (usually 80% or greater decrease) and resulted in a decrease in blood pressure rather than the 30% increase which is normally seen. During emersion the above pretreatment resulted in a modest (12%) increase in HR above predive values and a much lower BP compared to the predive values. Treatment with AH1 had little additional effect on BP during the dive or emersion states. However, after AH1 HR increased modestly during immersion and increased further after emersion when compared to the "an-autonomic" preparation. These results indicate that the fall in BP seen in the "an-autonomic duck" during diving and emersion is not due to release of histamine. However, histamine appears to be involved in the physiologic control of HR during diving and emersion. Supported in part by Minnesota SEA Grant # RS/5 #197, ONR #N00014-84-K-0224

13.3

SPECTRAL ANALYSIS OF HEART RATE VARIABILITY DURING EXPERIMENTAL ALTERATIONS IN BLOOD PRESSURE. Nassib G. Chamoun*, Eric L. Hagestad*, Richard L. Verrier and Bernard Lown*, Cardiovasc. Labs, Harvard School of Public Health, Boston MA 02115.

The power spectrum has been shown to provide a useful means of assessing the relative contributions of the two limbs of the autonomic nervous system to heart rate variability. Surgical denervation and pharmacological blockade have shown that fluctuations which occur above 0.1 Hz are due to the vagus, whereas those below 0.1 Hz are the result of mixed vagal and sympathetic activity. Little is known about the effect of heightened autonomic tone on the power spectrum. To determine the effect of baroreflex activation on power spectral density, heart rate variability of 8 anesthetized dogs was analyzed while their blood pressure was varied by nitroglycerin, controlled exsanguination and phenylephrine. *$p<0.05$vs control

| day | intervention | low frequency | high frequency |
|---|---|---|---|
| 1 | nitroglycerin | +189% | -95%* |
| 2 | exsanguination | -14% | -98%* |
| 2 | phenylephrine | +387%* | +508%* |

Thus, energy in the high frequency band correlates precisely with changes in vagal tone which result from alterations in systemic blood pressure. Spectral density in the low frequency band provides ambiguous information unless vagal activity is predominant. In conjunction with previous studies, these results suggest non-linear interactions between the sympathetic and parasympathetic nervous systems. More powerful methods will be necessary to define these relationships.

13.4

CARDIOVASCULAR AND RESPIRATORY EFFECTS OF ACETAZOLAMIDE ACTING AT A RESTRICTED SITE ON THE VENTRAL MEDULLARY SURFACE. P.G. Guertzenstein*, S.H. Andreatta*, and D.B. Averill. Dept. of Physiol. & Biophys., Inst. Ciencias Biomedicas, Sao Paulo, Brazil and Research Institute, Cleveland Clinic Foundation, Cleveland, OH, 44106.

Previous studies which have manipulated the neurochemical environment of the ventral medullary surface (VMS) at a site corresponding to the intermediate chemosensitive area have focused on the response of either cardiovascular or respiratory control systems. To investigate if these two effector systems are influenced by a common stimulus we applied acetazolamide (AZ), a carbonic anhydrase inhibitor, to this restricted region of the VMS. Cats (n = 13) were anesthetized with α-chloralose (60 mg/kg, i.v.) and the VMS exposed. Bilateral application of AZ (50 mg/ml) decreased blood pressure (BP) from 157 ± 3 mmHg to 96 ± 13 mmHg ($p < 0.001$) and reduced heart rate (HR) from 215 ± 6 bpm to 189 ± 6 bpm ($p < 0.01$). AZ consistently decreased minute ventilation. In 69% of the cats AZ produced apnea; in the majority of cases spontaneous breathing recovered before removal of the drug. We suggest that inhibition of carbonic anhydrase decreased tissue $[H^+]$ at a restricted VMS site and this had a concerted effect to decrease BP, HR and ventilation. The spontaneous recovery of ventilation may be mediated by increased peripheral chemoreceptor input or activation of central chemosensitive mechanisms. (S.H. Andreatta supported by FAPESP and FINEP.)

13.5

ROLE OF BARORECEPTORS AND CHEMORECEPTORS IN THE RESPONSE TO ACETAZOLAMIDE APPLIED TO THE VENTRAL MEDULLARY SURFACE. S.H. Andreatta*, D.B. Averill & C.M. Ferrario. Research Institute, Cleveland Clinic, Cleveland, OH.

Acetazolamide (AZ) may have a primary site of action at the intermediate chemosensitive area (IA) of the ventral medullary surface (VMS) to decrease blood pressure (BP), heart rate(HR) and ventilation. To investigate the contribution of peripheral baroreceptors and chemoreceptors to these responses, AZ (50 mg/ml) was applied to a IA of α-chloralose anesthetized (60 mg/kg) cats under three conditions: 1) intact baro- and chemoreceptors (n=4); 2) after sinoaortic denervation (SAD, n = 4); 3) assisted ventilation to maintain blood gases constant (n = 5). Under all three conditions similar decreases in BP were observed (-72 ± 10, -71 ± 25, -68 ± 17 mm Hg). When the influence of peripheral chemoreceptor input was removed by SAD or artificial ventilation, the HR responses (-31 ± 17 and -25 ± 11 bpm) were approximately one half that observed in the intact condition (-52 ± 16 bpm). In all three conditions AZ produced substantial decreases in diaphragm EMG or phrenic nerve activity. The data indicate that augmented peripheral chemoreceptor input as well as a primary central action of the AZ contribute to the larger HR response observed in the intact condition. Because the depressor and hypopneic responses were not substantially modified by SAD, the data emphasize AZ has a primary central site of action at the IA. (Supported in part by HL-31256 and HL-6835).

13.6

SENSITIZATION OF BARORECEPTORS FOLLOWING PULSATILE PRESSURE IS RELATED TO PULSATILE STRAIN. Mark W. Chapleau and Francois M. Abboud. Cardiovascular Center, University of Iowa College of Medicine, Iowa City, IA 52242

We have observed that multiunit baroreceptor activity (BA) at a constant level of static pressure (SP) is greater after exposure to a period of pulsatile pressure (PP) than before PP. The purpose of this study was to determine if post-PP sensitization measured as a decreased pressure threshold (Pth) occurs in single units and to determine if it is related to pulsatile strain or to the change in BA in response to PP. Unit BA (n=5) was recorded from the isolated carotid sinus (CS) in chloralose anesthetized dogs. CS diameter was measured by sonomicrometry during SP and PP (n=4). Pth's were determined by slow ramp increases in CS pressure (<2 mmHg/sec) both before and after several minutes of pulsation at a PP of ~35 mmHg. At low CS pressure (<50 mmHg) pulse diameter averaged 771±76 μm; Pth decreased from 86±9 mmHg before PP to 75±6 mmHg after PP (P<0.05). At moderate CS pressure (100 mmHg) pulse diameter averaged 424±17 μm; Pth decreased from 100±7 mmHg before PP to 88±6 mmHg after PP (P<0.05). At high CS pressure (150 mmHg) pulse diameter was minimal (245±32 μm); Pth was not altered after PP (108±6 vs. 109±5 mmHg). The shift from SP to PP increased BA at low pressure, decreased BA at moderate pressure, and did not change BA at high pressure. These results indicate that sensitization of single unit baroreceptors following a period of PP is related to pulsatile strain and not to the change in BA in response to PP. (HL14388)

13.7

THE ROLE OF ENDOTHELIUM IN ACTIVATION OF THE ARTERIAL BAROREFLEX. Timothy S. Axtelle*, Mark W. Chapleau, Thomas S. McDowell* and Francois M. Abboud. Cardiovascular Center, University of Iowa College of Medicine, Iowa City, IA 52242

Stretch of endothelial cells during increases in arterial pressure can initiate the formation of endothelial factors including prostacyclin ($PGI_2$). The purpose of this study was to test the hypothesis that endothelial formation of prostaglandins (e.g. $PGI_2$) may contribute to the activation of baroreceptors during increases in arterial pressure. In 10 anesthetized rabbits (chloralose) the aortic and vagus nerves were cut and the carotid sinuses were isolated and connected to a pressure reservoir. Baroreflex inhibition of lumbar sympathetic nerve activity (LSNA) was measured during step increases in carotid sinus pressure (CSP). Indomethacin (INDO, n=5) and aspirin (ASP, n=5) were placed in the isolated carotid sinuses. The maximal % inhibition of LSNA during elevation of CSP was 70±4% (SE) before and 68±4% and 49±13% (P<0.05) after each of 2 doses of INDO (40 and 80 μM, respectively). Corresponding values before and after 2 doses of ASP (1.0 and 2.0 mM) were 68±7%, 62±6% and 49±8% (P<0.05). Thus, blockade of cyclo-oxygenase attenuated the baroreflex control of LSNA. These results suggest that endothelial prostaglandins contribute significantly to the activation of arterial baroreceptors and the baroreflex. (Supported by HL14388)

13.8

REFLEX CONSTRICTION OF HUMAN FOREARM AND CALF RESISTANCE VESSELS TO HEAD LOWERING IN THE PRONE POSITION. L.K. Essandoh*, D. Duprez*, J.T. Shepherd. Mayo Clinic, Rochester, MN 55905.

Recent studies have indicated that, in response to a simulated postural change (application of lower body negative pressure of 15 mm Hg or less) and to sitting upright, there is the expected reflex constriction of the resistance vessels of the forearm but, unexpectedly, not of those of the calf. To see if there were other maneuvers that cause a similar reflex constriction in both vascular beds, forearm and calf blood flows were measured simultaneously by strain-gauge plethysmography before, during, and immediately following three minutes of "head-down-neck-flexion". Control flows were measured with the subject lying prone and the chin resting on a padded support at the rostral edge of the table in order to produce near maximal extension of the neck. The chin support was then removed, and the subject flexed and maximally lowered the neck. Recovery flows were measured following the return of the neck to its original position. There was no change in arterial blood pressure or heart rate with this maneuver; forearm and calf flows were reduced by 38% and 43%, respectively. The reduction in flow was immediate, suggesting that it is reflexly mediated. Neck flexion alone, or venous congestion of the head and neck, without a change in head level did not alter the blood flow. These studies demonstrate that, given the right reflex stimulus, the forearm and calf vessels respond similarly. Supported by NIH Grant #HL5883.

13.9

EFFECTS OF CHANGES IN [EPINEPHRINE] AND [SODIUM] ON FIRING CHARACTERISTICS OF A- AND C-FIBER CAROTID BARORECEPTORS. J.L. Seagard, C. Dean*, H.F. van Brederode*, F.A. Hopp*, E. Elegbe*, and J.P. Kampine. VA Center and Depts. Anes. and Physiol., Med. Col. Wisconsin, Milwaukee, WI 53295

Changes in sympathetic efferent nerve activity or exposure to different concentrations of epinephrine (EPI) or sodium (Na) have been found to alter firing of baroreceptors. This study was performed to determine the fiber type (A versus C) of baroreceptor afferent fibres sensitive to changes in [EPI] or [Na], using conduction velocities. Single fiber baroreceptor recordings were obtained from the left carotid sinus nerve (CSN) following vascular isolation of the carotid sinus (CS) to permit exposure of the baroreceptors to altered levels of [EPI] ($10^{-8}$-$10^{-6}$M) and [Na] (130-145mM). Ramps in CS pressure were used to stimulate the baroreceptors and a stimulus (CS pressure)-response (CSN activity) curve was obtained for each afferent fiber for control and each level of [EPI] or [Na]. In general, slower C-fiber baroreceptors (0.67-1.9 m/s) showed a greater response to elevations in [EPI] and [Na], with increases in threshold and saturation firing rates. The stimulus response curves were generally sigmoidal in shape, although the firing patterns were often irregular and pulsatile. The more exponential curves of the faster A-fiber baroreceptors (4.2-15 m/s) mainly exhibited increases in saturation firing rates. These results suggest that C-fiber carotid baroreceptors are more sensitive to changes in [EPI] and [Na] than A-fiber receptors. Supported by VA 7759-02P.

13.10

CARDIOVASCULAR RESPONSES TO BILATERAL CAROTID OCCLUSION (BCO) BEFORE vs. AFTER INNOVAR IN INTACT DOG. D.C. Randall, D.E. Fitzovich, J.G. Felker* & K.A. Ogilvy*. Dept. Physiol. & Biophy., Univ. of Kentucky Coll. Med., Lexington, KY 40536

We report the effects of the sedative/analgesic Innovar (0.4 mg/ml fentanyl & 20 mg/ml droperidol; 0.05 mg/kg) on the chronotropic and inotropic responses in dog (n=7) to 30 sec. BCO (implanted occluders). Data (mean ± SD) were recorded 2 weeks after surgery for a 30 sec. control and a 30 sec. BCO.

| | pre-Innovar | | post-Innovar | |
|---|---|---|---|---|
| | control | BCO | control | BCO |
| HR | 64 ± 14 | 76 ± 21 | 77 ± 25 | 86 ± 31 |
| BP | 85 ± 16 | 104 ± 26 | 76 ± 6 | 88 ± 14 |
| d(LVP)/dt | 3044 ± 472 | 3185 ± 529 | 3573 ± 780 | 4018 ± 972 |

Innovar increased control d(LVP)/dt ($p < .01$). The average increase in d(LVP)/dt during BCO was also significantly ($p < .01$) larger after drug administration. Conversely, the pressor response was smaller ($p < .01$) after Innovar. We conclude that Innovar has modest, though significant, effects upon this autonomic reflex response. Nevertheless, this drug may be appropriate in studies of the autonomic control of the circulation when use of totally awake subjects is not possible. (Supported by NIH grant HL 19343)

13.11

ELECTRICAL STIMULATION OF MUSCLE AND SKIN AFFERENT C-FIBERS INCREASES CORONARY ARTERIAL RESISTANCE.

K.H. Pitetti, G.A. Iwamoto, G.A. Ordway, and J.H. Mitchell. Univ. of Texas Health Science Center, Dallas, TX 75235

We described previously that electrical stimulation of the tibial nerve, which includes muscle and skin C-fiber afferents, increased coronary arterial resistance. In the present study, we sought to determine if stimulation of either muscle or skin C-fiber afferents individually would produce similar results. We studied the effect of electrical stimulation of the quadriceps (muscle) or saphenous (skin) nerve on left circumflex coronary arterial (LCCA) resistance in dogs. A constant flow preparation was used to assess changes in LCCA pressure and resistance during electrical stimulation before and after cooling the nerve to 2-4°C. Based on our recordings of the compound action potential, cooling the nerve to this temperature could be assumed to eliminate activity in myelinated fibers. Stimulation (20 Hz) of the quadriceps or saphenous nerve at 20, 70, 100 or 200 times the voltage threshold that evoked a recognizable compound action potential significantly ($p<0.05$) increased LCCA resistance, heart rate (HR), and systemic arterial pressure (SAP). Stimulation at 3 or 5 times threshold had no effect on the same cardiovascular parameters. Cooling the nerve to 2-4°C attenuated but did not abolish the increase in LCCA resistance, HR, and SAP that were evoked by stimulation at 200 times voltage threshold. These results demonstrate that stimulation of either muscle or skin afferent C-fibers increases coronary arterial resistance.

13.12

CARDIAC SYMPATHETIC AFFERENT CELL BODIES LOCATED IN THE PERIPHERAL AUTONOMIC NERVOUS SYSTEM.

Zeljko J. Bosnjak and John P. Kampine. Departments of Anesthesiology and Physiology, Medical College of Wisconsin and VA Medical Center, Milwaukee, WI 53295

This study was designed to determine whether chronic decentralization (2-3 weeks) of the stellate ganglion in eight cats would abolish sympathetic cardiac afferent nerve activity recorded at the stellate-cardiac nerve, and abolish local thoracic reflexes which are generated by stimulation of peripheral nerves (J. Physiol. 324:273, 1982; Am. J. Physiol. 246: R354, 1984; 248:R288, 1985). The ansae subclaviae, $T_3$ and $T_4$ rami, and the stellate ganglion were also examined under electron microscope for the extent of Wallerian degeneration. Afferent cardiac activation of the axon collaterals arising from cell bodies located in the dorsal root ganglia therefore was abolished due to degeneration. Sympathetic afferent nerve activity from the left ventricular receptors was still present and was recorded from the stellate cardiac nerve in all eight cats. Cardiac receptors were sensitive to mechanical distortion, increases in the left ventricular pressure, and epicardial application (or ventricular injection) of nicotine hydrogen tartrate salt and veratrine hydrochloride. These data imply that cardiovascular afferent input to the stellate ganglion persists following chronic decentralization and that sensory neurons are located in the peripheral sympathetic nervous system. Regulation of the heart occurs in part via thoracic ganglia independently of the central nervous system.

## EXERCISE PHYSIOLOGY

14.1

THE RESPONSE OF MATURE SP-SHR GROUPS TO MODERATE TREADMILL EXERCISE: PRELIMINARY RESULTS.

C.M. Tipton, S. McMahon* and E. L. Pauli.* Department of Exercise and Sport Sciences, University of Arizona, Tucson, AZ 85721

Previous results with very young SP-SHR groups performing either voluntary wheel (Overton et al., **JAP**, in press) or treadmill exercise (unpublished) has shown that exercise training did not lower the rise in caudal artery resting systolic blood pressure (RSBP) that occurs with time or significantly alter their life spans. To determine whether the effects of the high salt diet (3.7 mg/g) or the 1% NaCl drinking solution on RSBP were modified by the maturation status of the animal, equal numbers of males (M) and females (F) SP-SHR (N=48) were assigned to moderately trained (T) and non-trained (NT) groups after 134 days of age. At 180 days of age, the M-T had $\dot{V}O_2$ max values ($85\pm2$ ml·min$^{-1}$·kg$^{-1}$) that were 10.3% higher than the M-NT, and the F-T had run times ($8.9\pm0.3$ min.) that were 20.2% longer than the F-NT. By 204 days of age, only 14 of the 48 rats had died with more F-T dying than any of the other groups. RSBP ($\bar{X}$, SE, mmHg) results were as follows:

| Age (Days) | 134 | 162 | 180 | 204 |
|---|---|---|---|---|
| M-NT | 174 ± 2 | 230 ± 2 | 249 ± 5 | 259 ± 3 |
| M-T | 178 ± 2 | 229 ± 3 | 245 ± 4 | 256 ± 3 |
| F-NT | 155 ± 2 | 217 ± 4 | 242 ± 4 | 254 ± 3 |
| F-T | 157 ± 3 | 223 ± 5 | 241 ± 3 | 258 ± 3 |

These data suggest biological maturation does have a marked influence on the mortality of SP-SHR groups but does not modify the conclusion as to the effects of moderate exercise training on RSBP.

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14.2

POST-EXERCISE HYPOTENSION IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR).

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Blood pressure is reduced following rythmic exercise by hypertensive subjects (Wilcox et al., Br. Med. J. 285:767, 1982). The purpose of the current study was to determine if post-exercise hypotension could be documented in SHR following treadmill exercise. SHR were instrumented with Doppler flow probes and a carotid catheter. After recovery, animals were placed on the treadmill for stabilization of heart rate (HR) and mean arterial pressure (MAP). After at least 60 minutes of resting, animals were exercised for 20 (N=9) or 40 (N=7) minutes at 16.1 m/min. Changes in mesenteric (MR) and iliac (IR) resistances were calculated from MAP and blood flow data. Values (x ± SE) below are just prior to, and 30 minutes following, cessation of exercise (* = $p < 0.05$, ° = $p < 0.10$).

| 20 min | MAP (mmHg) | HR (bpm) | MR (Δ%) | IR (Δ%) |
|---|---|---|---|---|
| Pre | 163 ± 6 | 358 ± 8 | - | - |
| Post | 154 ± 6* | 358 ± 10 | -3 ± 6% | -11 ± 8% |
| 40 min | | | | |
| Pre | 151 ± 4 | 356 ± 3 | - | - |
| Post | 135 ± 5* | 340 ± 8° | -7 ± 8% | -6 ± 7% |

Although resistance data was quite variable, relative reductions were comparable with changes in blood pressure following exercise. In conclusion, post-exercise hypotension is seen following treadmill exercise by SHR, although the mechanism for this change remains unclear.

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14.3

INFLUENCES OF STATIC HANGING EXERCISE ON SP-SHR

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Although hypertensive populations are repeatedly cautioned against performing static exercises, there is a paucity of experimental data on the subject. Therefore, a forelimb hanging training (Ha) study was initiated with male (M) and female (F) stroke-prone hypertensive rats (SP-SHR). They were assigned to matched hanging (H) or non-hanging (NH) groups, fed Funabashi chow (3.7 mg Na/g) and tap $H_2O$ for 14-15 weeks after which a 1% NaCl drinking solution was provided until the 20th week. Ha, which caused an acute rise in HR of 112 ± 16 beats/min. and MBP of 68 ± 15 mmHg, consisted of suspending H and holding NH over an electrical grid that was associated with high frequency sounds. Ha (4-5 times weekly) consisted of 3 sets of 6-10 hangs lasting 7-10 sec/hang. Timed Ha tests with weights suspended indicated H groups held 2.2 times longer than NH groups. Caudal artery resting systolic blood pressure (RSBP) was secured at regular intervals (X, SE) and indicated that Ha by any group did not result in significant group differences after 15 weeks (F-H = 187 ± 5; F-NH = 181 ± 4; M-H = 188 ± 5; M-NH = 192 ± 4) nor after 20 weeks (F-H = 220 ± 4; F-NH = 222 ± 4; M-H = 228 ± 4, M-NH = 221 ± 6). Heart and bicep weights, plasma insulin levels, and blood volumes did not reveal significant group or sex differences. We concluded that this type of static exercise training had no consistent effect on RSBP and related parameters.

Supported in part by NIH Grant HL 33782-02

14.4

CARDIOVASCULAR RESPONSES TO A PHENYLEPHRINE INFUSION: EFFECT OF EXERCISE TRAINING MODALITY.

M.L. Smith, D.L. Hudson, H.M. Graitzer and P.B. Raven. Depts. of Physiol. and Med., TCOM, Ft. Worth, TX 76107.

Previously, we found that endurance trained (ET) men regulate blood pressure less effectively than sedentary men (UT), and these differences were due in part to differences in the baroreflex responsiveness. As Tesch et al. have reported that resistive exercise training improved tolerance to centrifugation, the question remains as to whether weight training alters blood pressure regulation. This study was designed to compare baroreflex function of competitive weight-trained(WT) men with ET and UT men. Thirty healthy men ($\bar{x}$ age=27±2 yrs) were studied. The cardiovascular responses to incremental infusions of phenylephrine to a maximum dose of 120 μg/min were evaluated in three subject groups (ET, UT and WT). The ΔHR/ΔSBP response was significantly less in ET ($\bar{x}$=0.47±0.1) than in UT ($\bar{x}$=0.82±0.2) or WT ($\bar{x}$=0.90±0.2) at $p<.01$, with no difference observed between UT and WT. No differences were observed in forearm blood flow, forearm vascular resistance and peripheral vascular resistance between any groups. These findings suggest that resistive exercise training does not alter normal baroreflex function in men, while supporting the hypothesis that endurance exercise training attenuates baroreflex responsiveness.

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14.5

HEART RATE SPECTRAL ANALYSIS IN EXERCISING HUMANS. C.S.Garrard, L.McAlpine*, A.Seidler* and D.Gordon*. College of Medicine, University of Illinois, Chicago.

The autonomic nervous system regulation of the heart was assessed on two occations by heart rate spectral analysis (HRSA) in 8 healthy volunteers exercising on a cycle ergometer. Heart rate was recorded by precordial ECG electrodes, and ventilation by face mask and Fleisch pneumotachograph. The spectral density of the beat to beat heart rate within the frequency bands 0.04-0.10 Hz (low-fr area, = sympathetic and parasympathetic activity) and 0.22-0.28 Hz (Hi-fr area, = parasympathetic activity, entrained by respiration) was calculated by fast-Fourier transform. After an initial rest period, subjects exercised with 25 watt incremental increases in work load each 5 min with intervening rest periods. Group mean heart rate increased from 77 to 116 beats /min, and the repiratory frequency increased from 0.23 to 0.30 Hz. Group mean Low-fr area decreased significantly with exercise from 6.5 ± 4.9 to 2.4 ± 1.4 ($p<0.001$, ANOVA). Hi-fr area also decreased from 2.7 ± 2.4 to 0.8 ± 0.9 ($p<0.001$, ANOVA). Results are consistent with decreasing sympathetic and parasympathetic modulation of heart rate variability during exercise induced tachycardia.

14.6

EFFECT OF AEROBIC EXERCISE TRAINING ON THE VALSALVA RESPONSE IN NORMAL MALES. James J. Smith, Jill A. Barney*, Leanne Groban*, Lois M. Sheldahl*, Felix E. Tristani* and Scot G. Levandoski*, VA Medical Center and Dept. of Physiology, Medical College of Wisconsin, Milwaukee, WI 53295.

Recent evidence suggests that aerobic exercise training (ET) may alter autonomic reaction to non-exercise stress. We investigated this further by analysis of the heart rate response to the Valsalva maneuver in thirteen healthy male subjects, 34 to 71 years of age, before (BT) and after (AT) a 6 month ET program. $\dot{V}_{O_2}$max increased from 32.9±1.1 (BT) to 40.2±1.5 ml/kg/min (AT)($p<0.001$).

The most sensitive HR indices to the Valsalva (the relation between $HR_{max}$ of Phase III and $HR_{min}$ of Phase IV) were analyzed in the 40 mm Hg, 15 second, supine maneuver. The mean individual HR differences (III-IV) increased 5.8±2.9 beats/min and the HR ratios (III/IV) increased by 0.20±0.06 ($p<0.01$) following ET. There was a positive correlation between the change in $\dot{V}_{O_2}$max values and the change in the III-IV delta heart rate pre and post ET ($r=+0.71$; $p<0.01$). The III-IV HR/$\Delta$T(between III to IV peaks) increased from 4.9±1.2 beats/sec to 7.2±1.9 beats/sec (n.s.) suggesting an increased rate of change of HR. Age did not influence the HR responses. The data suggest that aerobic exercise training increases the HR responsiveness to the Valsalva maneuver in normal human subjects.
(Supported by the VA, grant #8528 and AHA/Wisc. affiliate, grants #83-GA-55 and #85-GA-64.)

14.7

EFFECTS OF MUSCLE TEMPERATURE ON MAXIMAL INSTANTANEOUS POWER IN MAN. M. Ishii*, G. Ferretti*, C. Moia* and P. Cerretelli. Dept of Physiology, C.M.U., Rue Michel-Servet, 1, 1211 Genève 4 (Switzerland).

The maximal instantaneous anaerobic power of man ($\hat{w}$) as determined during a high jump off both feet on a force platform may be an indicator of the maximal splitting rate of ATP in the muscles of the lower limbs. The latter may change as a function of the ATP concentration and/or of physico-chemical changes at the muscle level. As a consequence, temperature may play an important role in determining $\hat{w}$. This hypothesis was tested in a group of subjects differently trained, all very familiar with the experimental set-up. After a series of control measurements at ambient temperature, the subjects, whose vastus lateralis temperature (Tm) was continuously monitored by a thermocouple inserted 3 cm deep in the muscle, sat in a thermoregulated water bath at 20 ± 0.2 °C for 1 hour until Tm attained 27.1 ± 0.2°C when the $\hat{w}$ measurements were repeated. The control Tm and $\hat{w}$ values ranged from 33,7 to 36,6°C and from 48.7 to 65.5 $W.kg^{-1}$, respectively, i.e. within normal limits. Following cold exposure, Tm decreased by 8.0 ± 1.0 °C and w by 31% ± 8 (n=6), i.e. for a given constant efficiency ($\eta$) value, less than expected on the basis of the usually assumed figure of $Q_{10}$ of 2 to 3. This seems to indicate that either actual $Q_{10}$ is less than 2 or that $\eta$ increases with decreasing Tm.
(Supported by the Swiss National Funds for Scientific Research, Grant No. 3.364-0.82)

14.8

MORPHOLOGICAL DIFFERENCES IN SKELETAL MUSCLE WITH AGING IN NORMALLY ACTIVE HUMAN MALES AND IN WELL-TRAINED COUNTERPARTS. J. Melichna*, C. Zauner, L. Havlikova*, J. Novak*, D. Hill* and R. Colman*. Karlova University, Prague, Czechoslovakia and Mt. Sinai Medical Center, Miami Beach, FL, 33140.

Thirty-three male athletes and 42 normally active male volunteers granted informed consent and served as subjects. They were assigned to younger (≤25.5 yr) and older (>25.5 yr) sub-groups. Samples were taken from m. vastus lateralis. Slow oxidative (SO), fast glycolytic (FG) and fast oxidative-glycolytic (FOG) fibers were identified by standard methods. Significance of differences was accepted when $P<0.05$. Athletes had larger mean diameters of the three fibers than did controls. A greater mean diameter of SO fibers was seen in older as opposed to younger athletes. Older controls had a smaller mean FG diameter than younger controls. Athletes as a group had a smaller mean percentage of FOG fibers and a greater mean percentage of SO fibers than did controls. There was a greater mean percentage of SO fibers in older as opposed to younger controls, but not so in the case of athletes. Mean percentage of FG fibers in older controls was only 64% of that in younger controls, but FG percentage in older athletes was 96% that in younger athletes. Characteristics of the athlete may include larger fibers and greater percentage of SO at the expense of FOG fibers. Atrophy of fibers with aging might be retarded by training which may also reduce the age-associated rate of FG percentage "loss" and SO percentage "gain".
(Supported by the National Academy of Sciences).

14.9

EFFECTS OF ELECTRICAL STIMULATION ON MAXIMAL CONTRACTION STRENGTH OF PARETIC MUSCLE. F.J. Servedio*, A. Servedio*, G.M. Davis*, V. Stull*, A.G. Suryaprasad*, S.C. Gupta* and R.M. Glaser. Wright State University School of Medicine, Miami Valley Hospital, V.A. Medical Center, Dayton, OH 45435

Electrical stimulation (ES) has been shown to supplement voluntary exercise in an able-bodied population at small percentages of maximal (max) effort (Servedio et al., 1985). The present study examined the effects of ES on max effort in a group of patients whose ability was limited due to head trauma or incomplete spinal cord injury. Strength tests (Cybex) at 0, 18 and 30 degrees/sec were conducted on the quadriceps (quad) muscles. Six (2M, 4F) subjects (S) were recruited ($\bar{x}$ age = 31.5 ± 9.6) and data were only collected on legs which exhibited some voluntary movement (n=10). S performed ES-induced contractions, max voluntary contractions (VOL) and VOL combined with ES (HYBRID). Max tolerable level of ES was determined by gradually increasing stimulation intensity (square wave pulses, 300 usec duration at 35 HZ) across 2 surface electrodes placed over motor points of the quad. Results were:

| | ES (N) | VOL (N) | HYBRID (N) |
|---|---|---|---|
| 0 deg/sec | 20.2 ± 3.7 | 36.9 ± 9.1 | 42.4 ± 9.4 |
| 18 deg/sec | 20.9 ± 5.8 | 37.3 ± 11.5 | 49.2 ± 12.3 |
| 30 deg/sec | 16.0 ± 4.7 | 34.6 ± 11.3 | 51.7 ± 12.1 |

These data suggest that hybrid (VOL + ES) exercise permits a higher intensity of strength training in paretic muscles.
(Supported in part by V.A. Rehab. R & D Service)

14.10

MUSCLE CHEMOREFLEX CONTROL OF SYMPATHETIC NERVE ACTIVITY DURING EXERCISE IN HUMANS. D.R. Seals*, S.L. Stringer* and R.G. Victor* (SPON: J.H. Mitchell). Moss Heart Ctr, Univ. of Texas Hlth Sci Ctr, Dallas, TX 75235; Univ. of Arizona, Tucson, AZ.

The goal of this study was to isolate the autonomic effects of muscle chemoreflexes from those of central command and mechanoreceptor reflexes during exercise in humans. Using electromyographic (EMG) activity as an index of central command (voluntary motor unit activation), we performed direct measurements of muscle sympathetic nerve activity (MSNA) with microelectrodes in the peroneal nerve and recorded mean arterial pressure (MAP), heart rate (HR), and force of contraction in 7 healthy subjects during 3 min of ischemic and non-ischemic rhythmic handgrip (RHG) at the same level of forearm EMG activity (35% max). During non-ischemic RHG, MSNA did not change. In contrast, during ischemic RHG at the same level of EMG activity (same central command), MSNA increased dramatically by 135±37% ($\bar{X}$±SE, $p<.05$) despite a 3-fold greater fall in force (less mechanoreceptor activity) from the 1st to 3rd min of ischemic vs non-ischemic RHG (49±11% vs 16±4% decrease, $p<.05$). The increases in MAP (25±2 vs 10±2 mmHg) and HR (30±2 vs 12±1 bpm) were also greater ($p<.05$) during ischemic vs normal RHG. Since central command was presumably equivalent in both conditions and mechanoreceptor stimulation was less during ischemic vs non-ischemic handgrip, we conclude that the augmented responses in sympathetic activity, arterial pressure, and heart rate during ischemic exercise were caused by activation of muscle chemoreflexes.

14.11

Maximal Capillary Diffusion Capacity and Myocardial Capillarity in Exercise Trained Dogs. M. H. Laughlin and R. J. Tomanek Dept. Biomed. Sci. and Dalton Research Center, UMC, Columbia, MO 65211 and Dept.Anat., Univ. of Iowa, Iowa City, IA 52242.

Our purpose was to determine if changes in myocardial capillarity are associated with the exercise training induced increases in coronary transport capacity we've seen in dogs. The approach was to measure maximal capillary diffusion capacity (CDC) in working hearts and then measure capillary numerical density (CN) capillary surface area density (CSA) and capillary volume density (CV) in specimens from perfused-fixed hearts. 8 dogs (20-30Kg) were exercise trained (ET) for 12-18 wks. with the program designed by Tipton. The control group (C) consisted of 7 normal dogs. CDC for $Cr^{51}$-EDTA was determined during maximal adenosine coronary vasodilation with perfusion pressures equal to 100 (torr) in both groups. The ET dog's CDC was 58±10 ml/min/100g which was significantly greater than the control value (31±6). Maximal CDC was linearly related to CV (r=.61) and CSA (r=.78) However, there was no difference between ET and C left ventricular CN, CSA, CV or intercapillary distance. The data indicate that, while coronary blood flow capacity and capillary transport capacity may be improved in ET dog hearts, these changes are not associated with an increase in myocardial capillarity. Rather, the increased CDC appears to be due to changes in capillary blood flow. Supported by NIH grants HL-18629, HL-36531 and HL-01774.

## CARDIAC DYNAMICS

15.1

CARDIAC RESPONSES TO LEFT ATRIAL MECHANORECEPTOR STIMULATION William B. Wead, Andrew M. Roberts and Michael A. Kurz*. Dept. of Physiology, Univ. of Louisville, Louisville, KY 40292.

The purpose of these experiments was to study the cardiac responses and autonomic reflex pathways involved with stimulation of the low pressure mechanoreceptor of the left atria. A small balloon was positioned in the left atrial appendage of ten, anesthetized, open-chested dogs. Rapidly injecting warm saline into the balloon, distended the left atrial appendage and produced a reflex increase in heart rate of 77.5±7.1% and a 31.7±4.6% increase in left ventricular contractility (Vmax). Left atrial distension in dogs whose hearts were being paced produced a 22.1±6.2% increase in Vmax. Bilateral vagotomy by cooling (0°C) or sectioning, eliminated any reflex increase in heart rate but had little effect on the increase in Vmax (22.6±3.7%). After bilateral sectioning of the stellate ganglia, distension of the left atrial appendage failed to produce any changes in Vmax. Our data suggest that stimulation of the left atrial mechanoreceptors causes a reflex increase in heart rate with afferents that are vagally mediated and an increase in contractility which is mediated by sympathetic pathways and not dependent on the increase in heart rate.
(Supported in part with funds from the American Heart Association, Kentucky Affiliate, and the American Lung Association.)

15.2

REGIONAL MYOCARDIAL CONTRACTILITY ASSESSED BY WORK-AREA AND WORK-LENGTH RELATIONSHIPS. I. Krukenkamp*, N. Silverman, S. Levitsky. Univ. of IL, Chicago, IL 60680

In 10 canine hearts, piezoelectric dimension transducers were placed in the anterior subendocardium 1 cm apart, both perpendicular and parallel to fiber shortening. During incremental volume loading on right heart bypass, the following relationships were inscribed before and after infusion of phenylephrine (2µg/kg/min): (1) Regional stroke work vs. end diastolic area (RSWA) or length (RSWL) (2) End systolic pressure vs. regional area (ESPRAR) or length (ESPRLR). Based on the variability of these data, the minimal detectable difference (MDD, % of control) at a 95% confidence level was determined.

| | CONTROL | | Phenylephrine | | MDD |
|---|---|---|---|---|---|
| | Slope † | r | Slope † | r | |
| RSWA | 102±8 | .876 | 110±12* | .943 | 25 |
| ESPRAR | 5.8±1.2 | .796 | 5.5±1.7* | .820 | 83 |
| RSWL | 83±8 | .852 | 100±18* | .922 | 73 |
| ESPRLR | 63±13 | .726 | 49±11* | .809 | 200 |

Data: mean±sem; * NS vs control by ANOVA; †mmHg/beat/(mm)

All relationships were linear with the slope reflecting an afterload independent index of contractility. However, the potential sensitivity of RSWA to discriminate changes in regional function render it superior to alternative indices.

15.3

POWER SPECTRUM ANALYSIS OF THE SECOND SOUND OF THE PHONOCARDIOGRAM IN LOW CARDIAC OUTPUT STATES. A.B. Knight, M.D., R.T. Fulfer, M.D., and C.H. Williams, Ph.D.* TTUHSC, El Paso, Tx. 79905

Cardiovascular function parameters determined with invasive techniques (Swan Ganz thermodilution catheter, central venous catheter, Millar microtip catheter) were compared with analysis of the power spectrum of the second sound of the phonocardiogram using the Fast Fourier Transform (FFT). Six normal pigs (average weight 20 kg) anesthetized with sodium thiopental were studied during $N_2O$/halothane anesthesia and acute hemorrhagic shock. Phonocardiogram recordings were obtained in the control situation and after stabilization in a low cardiac output state (DSP200 International Acoustics Incorporated) and the magnitude of the power spectrum of $S_2$ was plotted against frequency in the range 0-100 Hz. Results: In normal anesthetized animals with a cardiac output of 2.4±0.4 L/min. the FFT plot showed two major peaks at 17.0±2.4 Hz and 30.6±4.9 Hz, respectively. Ventilation with 2.5% halothane for 30 minutes decreased the cardiac output 1.7±0.3 L/min. and there was a significant shift of the frequency to 10.5±3.5 Hz and 22.4±7.7 Hz ($p < 0.0005$ and 0.0125), with progressive disappearance of the lower frequency peak. Acute hemorrhage to a cardiac output of 1.2±0.3 L/min. produced the same changes with a flattening of the first peak and a shift to 14.3±3.4 Hz and 20.6±4.0 Hz ($p < 0.025$ and 0.0005). There is a definite relation between the power spectrum of $S_2$ and changes in cardiac function.

15.4

NIFEDIPINE PROTECTS MYOCARDIAL CONTRACTILITY AND COMPLIANCE DURING ISCHEMIA. Y. Lebedinsky*, M. Wasicko*, J.K-J. Li* and G.F. Merrill. Programs in Physiology and Biomedical Engineering, Rutgers University, New Brunswick, NJ 08903.

Myocardial dysfunction during acute occlusion of a coronary artery is accompanied by 1) systolic bulging, 2) myocardial thinning, 3) diminished contractility and segmental shortening in the ischemic zone, and 4) hyperkinesis of the normal zone. We have recently shown that 15 min ischemia followed by an equal period of reperfusion in the canine myocardium is characterized by recovery of diastolic compliance (EDL/EDP) whereas contractility (segmental shortening % Δl) remains depressed. One objective of the present study was to examine the effects of nifedipine (3 ug/kg/min i.v.) on myocardial dysfunction during ischemia in anesthetized dogs (n=6). Results are presented below.

| | Ischemia (-nifed) | | | Ischemia (+nifed) | |
|---|---|---|---|---|---|
| | Control | 5 | 15 | 5 | 15 |
| Δl(%) | 16.0±28 | -7.9±2.3 | -7.4±3.6 | 3.2±1.2* | 5.1±2.1* |
| EDL/EDP (mm/mmHg) | 1.1±0.3 | 0.8±0.2 | 0.8±0.3 | 1.1±0.3* | 1.1±0.3* |

Means ± S.E.M, *P<0.05 relative to values in absence of nifedipine. In the presence of nifedipine ischemia-induced systolic lengthening (-shortening) did not persist, and ventricular compliance increased relative to that seen in the absence of nifedipine. We conclude that nifedipine significantly improves mechanical dysfunction accompanying brief periods of ischemia in the canine myocardium.

15.5

IN VIVO CHRONOTROPIC AND INOTROPIC EFFECTS OF DOBUTAMINE IN ALTERED THYROID STATES. M. Mullett*, P. Reifenrath* and D.M.Van Wynsberghe. Department of Biological Sciences, University of Wisconsin, Milwaukee, WI 53201

Previous in vitro studies have shown that myocardial receptor density is altered by altered thyroid states. In the present study, Dobutamine ($B_1$ agonist) and Atenolol ($B_1$ antagonist) were used to determine in vivo effects on heart rate (HR) and left ventricular +dP/dt (LV dP/dt) in euthyroid (E), hyperthyroid ($T_3$: 500 ug/Kg/day for 3 days) [$T_3$], and hypothyroid (surgically thyroidectomized) [Tx] rats. Dobutamine concentrations of 0.25 to 40 ug/Kg were given i.v. in the absence or presence of varying doses of Atenolol (0.125 - 2.5 mg/Kg). These dose-response curves resulted in dose related increases in HR and LV dP/dt in the E, $T_3$ and Tx states. Atenolol was more effective in blocking the chronotropic response to Dobutamine in the Tx than in the $T_3$ animals, suggesting an increase in myocardial $B_1$ receptor density in the $T_3$ group. Atenolol was also more effective in blocking the inotropic response to Dobutamine in E than in $T_3$ animals, again indicating increased receptor density in the $T_3$ state. The $EC_{50}$ for Dobutamine in the absence of Atenolol is lower for LV dP/dt than for HR, indicating that, in vivo, Dobutamine is primarily an inotropic agent with mild chronotropic effects.

15.6

MODULATION OF THE RESPONSE TO BILATERAL CAROTID OCCLUSION BY VARYING INSULIN LEVEL IN DOGS. D.F. Fitzovich & D.C. Randall, Dept. Physiology & Biophysics, Univ. of Kentucky, Lexington, KY 40536.

We have previously reported (Fed Proc 43:526,1984) the development of a preparation in conscious, chronically instrumented dogs in which insulin and glucose levels can be simultaneously manipulated. Insulin is first reduced below physiologically significant levels by Alloxan treatment, and then replaced by contiuous infusion via a tether system at a level which results in fasting normoglycemia. We now report the effects of altering insulin and glucose levels for one hour prior to performance of bilateral carotid occlusions (BCO, 30 sec. duration), in n = 4 dogs. Data are reported for 3 states characterized by plasma immunoreactive insulin level (IRI, ng/ml) and plasma glucose level (G, mg/100ml): (N) basal insulin infusion, IRI 0.15 ± 0.07, G 85 ± 8; (L) low insulin, IRI < 0.05, G 298 ± 20; and high insulin, normoglycemic (H), IRI 0.92 ± 0.10, G 104 ± 14. Cardiac responses were assessed by the maximum rate of rise of left ventricular pressure [d(LVP)/dt] and mean aortic pressure (MAP). Resting values of d(LVP)/dt (mmHg/sec) were: (N) 2513±112, (L)2957± 113, and (H)2700±173. BCO elicited increases of (N)104±15, (L)126±5,and (H)60±12. Resting values are signif. different (p<.05) between N and L, while the responses to BCO are different between N and H, but L is not signif. despite a tendency to be higher than N. MAP values were not signif but tended to decrease in H. (Supported by KY Heart Assoc. and NIH grant HL 19343.)

15.7

EFFECT OF DIETARY FISH OIL ON CARDIAC FUNCTION IN THE ISOLATED PERFUSED RAT HEART. Diane K. Reibel, Marie A. Holahan* and Carl E. Hock. Thomas Jefferson University, Phila.,PA. 19107 and University of Medicine and Dentistry of New Jersey-SOM, Camden, NJ 08103.

Rats fed 5% menhaden oil (MO) for 4 weeks exhibited no significant differences in body weights, heart weights, mean arterial blood pressure or in vivo heart rates when compared to rats fed 5% corn oil (CO). Hearts were isolated and perfused by the Langendorff procedure and subsequently as working preparations. During Langendorff perfusion spontaneous heart rates were significantly lower in hearts of rats fed MO (286±8 vs 324±10 beats/min, MO vs CO, respectively, p<0.05). There was no concomitant change in coronary flow. In electrically paced working hearts, peak systolic pressure was significantly higher (84±1 vs 76±2, MO vs CO, respectively, p<0.01). This was associated with no change in coronary flow rates while aortic flow rates tended to be higher in hearts of rats with MO feeding. The mechanism of these effects is not known, however, the fatty acyl composition of myocardial membrane phospholipids was markedly different in the two groups of rats. Specifically, the number of double bonds in the fatty acyl chains of total phospholipids was significantly elevated with MO feeding. Furthermore, the ratio of n-3/n-6 fatty acids was increased by approximately 10-fold. These dietary-induced alterations in membrane phospholipid composition may contribute to alterations in function in the isolated heart.

15.8

HEMODYNAMIC FUNCTION IN ACUTE PANCREATITIS. JW Horton and CA Burnweit*. University of Texas Health Science Center, Southwestern Medical School, Dallas, TX 75235-9031.

Acute pancreatitis(AP) is often associated with impaired cardiovascular(CV) function. This study examined the systemic CV effect of AP induced by injecting autologous bile (0.5 ml/kg) into the canine pancreatic duct. After AP was induced, 9 control dogs (Group 1) were given no resuscitation; lactated Ringer's was infused in 9 dogs (Group 2) to maintain mean arterial pressure(MAP) and pulmonary wedge pressure at control values. In unresuscitated dogs, MAP, cardiac output (CO), stroke volume(SV), and stroke work fell (p=0.05) while heart rate(HR) and peripheral resistance(PR) rose (p=0.05). All indices of CV function remained unchanged in Group 2. Neither dP/dt max nor dP/dt at a developed pressure of 40mmHg were depressed by AP in either group. Our data indicate that the detrimental effects of AP on CV function are related solely to hypovolemia and reduced cardiac filling, and not humoral and autonomic reflexes induced by the disease.

| GROUP | CONTROL | | 300 MIN AP | |
|---|---|---|---|---|
| | 1 | 2 | 1 | 2 |
| MAP, mmHg | 101±4 | 99±5 | 74±12 | 92±8 |
| CO, ml/kg | 118±7 | 129±6 | 56.2±11 | 128±9 |
| SV, ml/kg | 0.93±.08 | 1.18±.09 | 0.22±.07 | 1.26±.13 |
| HR, bpm | 125±7 | 110±4 | 185±10 | 99±5 |
| PR, dynes/sec/cm-5 | 3130±410 | 2965±360 | 4436±610 | 2933±40 |
| dP/dt, max mmHg/sec | 3193±375 | 2772±250 | 3320±750 | 2785±320 |
| dP/dt DP 40, mmHg | 2425±332 | 2175±217 | 2740±710 | 2275±325 |

15.9

PREVENTION OF EARLY MYOCARDIAL DYSFUNCTION WITH FLUID INFUSION IN SEPTIC RATS. Brenda E. Field,* Eric C. Rackow, Mark E. Astiz,* Timothy M. O'Toole,* Max H. Weil. The Chicago Medical School, North Chicago, IL 60064.

We previously reported that hearts isolated from septic rats have significant decreases in contractility (dP/dt). In the present study, the Langendorff isolated heart preparation was used to evaluate the effect of fluid therapy on dP/dt during sepsis. Arterial and venous catheters were inserted into anesthetized Sprague-Dawley rats. After measurement of BP, HR, and RR, sepsis was induced by cecal ligation and perforation in 9 animals. Five sham operated animals served as controls. Four of the 9 septic animals were treated with intravenous infusion of 5% albumin at 5 cc/hr, which maintained CVP and cardiac output at baseline levels in previous septic rat experiments using this model. The BP, HR, and RR were measured 3 1/2 hrs after surgery and the animals were sacrificed. The hearts were rapidly removed and placed in Krebs-Henseleit buffer at 4°C. A cannula was inserted into the aorta and a latex balloon into the left ventricle. The coronary arteries were perfused with oxygenated buffer at 37° through the aortic cannula. After 20 mins the balloon was filled to a standard preload and ventricular pressure recorded. In hearts from untreated septic animals, dP/dt was 1220±60 (SE) compared to 1920±280 mmHg/sec in hearts from treated septic animals (p<0.05) and 1780±110 in hearts from sham controls (p<0.01). These observations suggest that fluid infusion prevents early myocardial dysfunction during sepsis.

15.10

MAGNESIUM REVERSES THE ADVERSE EFFECTS OF ANGIOTENSIN ON CARDIAC PERFORMANCE IN THE DOG. Howard S. Friedman,Abdel M. Mokraoui*,Thach N. Nguyen*,Preetham Jetty*,Michael Denker*, Toshi Murakawa*,Burton M. Altura,SUNY Health Science Center at Brooklyn and The Brooklyn Hospital,Brooklyn,N.Y.

We have previously found that $Mg^{2+}$ reduces cardiac output and systemic and pulmonary pressures in the neurally-intact dog(Fed Proc,45:657;1986). Because $Mg^{2+}$ attenuates the vasoconstrictive effects of angiotensin II(angio)in isolated blood vessels,the influence of $Mg^{2+}$ on the cardiovascular effects of angio in neurally intact α-chloralose anesthetized dogs with rate and atrioventricular(A-V)conduction held constant by A-V sequential pacing was examined. The table summarizes the hemodynamic changes produced by angio,1-2 μg/min,before,during and 15 min after administration of MgCl2,1 mM/min.

| | Before | During | After |
|---|---|---|---|
| CO(L/min) | -0.6±0.2* | 0.6±0.2* | -0.2±0.1 |
| LVSP(mmHg) | 26±4* | -3±7 | 20±5* |
| MAP(mmHg) | 28±5* | -1±8 | 16±4* |
| LVEDP(mmHg) | 3±2 | 4±2 | 1±1 |
| CBF(ml/min) | -9±12 | 27±12 | -13±14 |

Changes of CBF after angio in the presence of $Mg^{2+}$ correlated with CO,r=0.69. Thus,the vasoconstrictive effects of angio are antagonized by $Mg^{2+}$. With heart rate controlled,$Mg^{2+}$ reverses the adverse effects of angio on cardiac performance. Abbreviations: CO-cardiac output;LVSP=left ventricular systolic pressure;LVEDP=left ventricular-end diastolic pressure;MAP= mean aortic pressure;CBF=coronary blood flow; *=P<0.05.

15.11

IS OXYGENATED TERMINAL CARDIOPLEGIA OF BENEFIT IN HYPERTROPHIED HEARTS AFTER PROLONGED CARDIOPLEGIC ARREST? Charles M. Peniston*, Paul A. Spence*, Carin Wittnich*, Haysam El-Dalati*, A Karim Jabr*, Samuel V. Lichtenstein*, and Tomas A. Salerno* (SPON: A. Slutsky). University of Toronto, Ontario, Canada M5B 1W8

Oxygenated terminal cardioplegia (TC) has been shown experimentally to reduce myocardial injury after prolonged aortic clamping in normal hearts but its effect in the hypertrophied heart is unknown. This study was designed to determine whether oxygenated terminal cardioplegia would better preserve left ventricular (LV) function after prolonged aortic clamping. Seventeen hypertrophied pigs (supracoronary aortic banding) were placed on cardiopulmonary bypass and the heart was isolated in situ. Baseline LV function was assessed with a compliant balloon. After 3 hours of multidose cold crystalloid cardioplegia (septal temperatured 8-12°C), the hearts were perfused with one of two oxygenated terminal cardioplegia solutions at 40 to 50 mmHg over a 10 minute period [Fluosol-DA-20% (OF) 5 pigs, Blood (OB) 6 pigs]. Six pigs received no terminal cardioplegia (C). LV function was reassessed at 60 minutes of normothermic reperfusion. RESULTS: When compared to crystalloid cardioplegia alone (C), there was no significance difference ($p>0.05$ ANOVA) in LV function or compliance in hearts subjected to oxygenated terminal cardioplegia (OF,OB).

| TC | Systolic pressure (% control) | Developed pressure (%control) | dP/dt (%control) | Diastolic pressure (% control) |
|---|---|---|---|---|
| OF | 77±6 | 62±7 | 45±9 | 187±20 |
| OB | 48±20 | 46±20 | 33±16 | 115±43 |
| C | 68±11 | 45±8 | 34±8 | 135±24 |

Mean-SEM, Balloon volume = 25 ml.

CONCLUSION: In the hypertrophied pig heart, oxygenated terminal cardioplegia was of no benefit in improving LV function.

## TEMPERATURE REGULATION AND HIBERNATION

16.1

HUMAN THERMOREGULATORY MODEL FOR UNCLOTHED IMMERSION DURING REST IN COLD WATER. P. Tikuisis*, R.R. Gonzalez, and K.B. Pandolf. Defence and Civil Institute of Environmental Medicine, Downsview, Canada M3M 3B9; US Army Research Institute of Environmental Medicine, Natick, MA 01760-5007.

A model of thermoregulation based on the concepts of Stolwijk and Hardy (Pflugers Arch 291, 129-162 (1966)) and Montgomery (Ann Biomed Eng 2, 19-46 (1974)) has been developed to simulate human physiological responses to cold-water immersion. Data were obtained from experiments where thirteen healthy male volunteers were totally immersed under resting and nude conditions for 1 h in water temperatures of 20 and 28°C. After 1 h of immersion, mean measured rectal temperatures ($T_{re}$) decreased by about 0.9 and 0.5°C in 20 and 28°C water for all subjects, yet mean metabolic rates (M) increased by about 275 and 90 W for the lean mass group (n=7) and 195 and 45 W for the normal mass group (n=6). Predicted values of $T_{re}$ and M within the standard error of the measured values were obtained by altering the previous models predominately in two areas: 1) the efferent command for shivering included thermal inputs from the skin independent of their inclusion with the central temperature; and 2) initial shivering was confined to the trunk region to avoid overly large predicted initial rates of rectal cooling. In addition, once the skin temperature had stabilized, the model determined convective heat loss by assuming zero rate of heat storage in the skin compartment, thus bypassing the theoretical determination through fluid dynamic considerations which is acutely sensitive to the skin-water temperature difference.

16.2

THERMOREGULATORY ADJUSTMENTS DURING 3-HOUR IMMERSION IN COOL WATER. Michael M. Toner*, Ellen L. Glickman*, Christopher C. Dunbar* and William D. McArdle* (Spon: Kent B. Pandolf). Department of Health and Physical Education, Queens College, Flushing, NY 11367

The present investigation examined the metabolic and thermal responses during immersion up to the neck of eight male volunteers in stirred water at 24, 26 and 28°C. Similar rectal temperature ($T_{re}$) values were observed for both the 26 and 28°C tests. $T_{re}$ declined for the first 1.5-2.0 h ($\Delta T_{re}$, 0.9 and 0.9°C, respectively; $P<0.05$); however, between 2.0-3.0 h, $T_{re}$ leveled off and remained unchanged ($\Delta T_{re}$, 0.1 and 0.1°C; $P>0.05$). In 26 and 28°C tests final $T_{re}$ values were similar (36.4 and 36.3 °C, respectively). Similar oxygen uptake ($\dot{V}O_2$) responses were seen for the 26 and 28 °C tests. Following an initial spike, $\dot{V}O_2$ gradually increased throughout the initial 1.5-2.0 h and plateaued thereafter ($\dot{V}O_2$, 26°C≅0.55 l/min, 28°C ≅0.50 l/min; $P>0.05$). Mean skin temperature ($\bar{T}_{sk}$) approached water temperature within the first 5 min in both 26 and 28°C (final $\bar{T}_{sk}$, 26.8 and 28.5°C, respectively; $P<0.05$). In 24°C, $T_{re}$ declined for the first 2.0-2.5 h ($\Delta T_{re}$, 1.8°C; $P<0.05$) whereas $T_{re}$ during the final 0.5 h remained unchanged ($\Delta T_{re}$, 0.0°C; final $T_{re}$, 35.8°C). $\dot{V}O_2$ responses showed a similar pattern though the plateau value was higher ($\dot{V}O_2$≅0.65 l/min) compared with both 26 and 28°C tests. These data suggest that despite the thermal strain of cool water, the thermoregulatory system is capable of maintaining $T_{re}$ but at lower values.

16.3

ROLE OF BODY FAT WORKING IMMERSED TO VARIOUS LEVELS IN 5, 7.5 & 10°C WATER. G.K. Gee* and R.F. Goldman. Corning Comm. College, Corning, NY 14830, and Multi-Tech Corp., Natick, MA 01760

We immersed 8 volunteers (2 Large, >45 kg/m², >25% fat; 5 Average, 37-38 kg/m², 16-20%; 1 Thin, 34 kg/m², 10.6%; 2 more Th withdrew D-1), in long-sleeved shirt, trousers, boots, helmet, and 10.5 kg mesh vest, for 3 hours at 5°C to knee level with wet and dry clothing; for 2 hours at 7.5°C to thigh and chest level and at 10°C to knee, waist and neck level (10'Rest-20'Work- 10'R-30'W, etc.); W = bench (43 cm), 10 steps/ min aided by hand hold atop the 1.8m high, 0.9m diameter constant T-$H_2O$ tank. Tre (removal at 35°C), 10 pt Ts (4 below waist, 2 torso, 4 arm/head), heat flow (HF - RdF sensors) at 5 sites and Metabolism (M) were measured. At 5°C, knee level, tolerance was shorter with wet than dry clothing (102 vs 118'); final Tre (37.6 vs. 37.5C) and $\bar{T}s$ (27.7 vs. 26.6C) were comparable. Initial M at rest = 75W; final M ≅450 W for L, 300W for A and 250W for Th Ss. Final HF ranged 315 to 500 W/m² for immersed area and ≅100W/m² unimmersed; A and Th Ss lost ~ 50W/m² more through unimmersed wet than dry clothing. One A exhibited "vasoconstriction exhaustion?" (HF >800 W/m²) at 90' with wet clothing; foot pain, numbness and inability to step were more common end points. At all levels in 7.5 and 10°C water, L Ss had lower relative M (W/kg) at work and rest; total M (W) was only lower at rest. L also maintained greater Tre-$\bar{T}s$ under all conditions and final Tre was higher than initial for 5°C (knee - wet or dry clothing), 7.5°C thigh, and 10°C knee immersions. Being L is advantageous in cold water; being small/thin requires unusual endurance for immersion: to knee in 5°C for 48' with wet (or 63' with dry) clothing; in 7.5°C to thigh for 45' or to chest for 33'; and in 10°C to waist for 69' or neck for 48'.

16.4

RESIDUAL EFFECT OF CLASSICAL CONDITIONING AS A TREATMENT FOR RAYNAUD'S DISEASE. D.E. Roberts, S. Jaber*, D. Kerr*, W. Beetham*. U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760-5007.

Previous studies have shown classical conditioning to be an effective non-invasive method of treatment of the cold hypersensitivity of idiopathetic Raynaud's disease. Treatment has consisted of a number of whole body cold exposures (0°C) while inducing warm hands by means of a waterbath (41°C). Treatment has been performed in a laboratory setting and also in an outpatient mode with each method having high success rates (85%). Subjective methods have been used to perform follow-ups and some subjects have indicated a positive effect for a year or longer. This study was designed to quantitate the response to a cold stress before treatment, after treatment, and after 3 months with no treatments. Fifteen subjects were treated (outpatient mode with an average of 42 treatments) and 8 were retested after 3 months. The 8 subjects had an average increase of 2.3°C in their digits following treatments when exposed to a standard cold stress (0°C/10 min) ($p < 0.01$). After 3 months of no treatment, the average digital temperature was 2.9°C greater than pre-treatment ($p < 0.01$). This data indicates that classical conditioning is effective immediately in most cases and a residual effect is present and perhaps enhanced after 3 months.

16.5

TRUNK vs. LIMBS HEAT LOSS IN RESTING AND EXERCISING MEN IN COLD WATER. Guido Ferretti*, Arsenio Veicsteinas and Donald W. Rennie. Depts. of Physiology, Universities of Geneva (CH), Brescia (Italy) and Buffalo (U.S.A.)

The amount of heat lost by the trunk ($H_T$), the limbs ($H_L$) and the whole body ($H_B$, included the head), by heat flow discs transducers, and the oxygen consumption ($\dot{V}O_2$) by indirect calorimetry, were measured on 4 young men fully immersed for up to 60 min in critical water temperature (Tcw) and below, at rest and during combined arms and legs exercise. At rest at Tcw, $H_T$ and $H_L$ averaged 51.5±5.7 (SD) W and 54.3±5.2 W respectively. For a mean $\dot{V}O_2$ of 0.33±0.07 l·min$^{-1}$, $H_B$ was equal to 116.5±10.5 W. Below Tcw, per each °C of decrease of Tw, $H_B$ increased by about 15 W, whereas $\dot{V}O_2$ remained constant. During exercise at Tcw ($\dot{V}O_2$=2.27±0.25 l·min$^{-1}$) $H_T$ and $H_L$ were 3.9 and 4.6 times higher than at rest; $H_B$ was equal to 480.3±61.8 W, and did not change as a function of Tw. It is concluded that: a) at rest the same amount of heat is lost by the trunk and the limbs; b) during exercise, independently on Tw, 40% and 55% of the heat is lost by the trunk and by the limbs, respectively. The relative high amount of heat lost by the trunk might be a consequence of convective heat transfer from the working muscles of the limbs.

16.6

VISCOELASTIC CHANGES IN ARTERIAL WALLS FOLLOWING COOLING. N. R. Bandick, K. L. Dargatz*, J. R. Smith* and D. E. Roberts, Western Oregon State College, Monmouth, OR 97361 and US Army Research Institute of Environmental Medicine, Natick, MA 01760

The object of this investigation was to determine if cooling the abdominal aortae and femoral arteries of rats from 37C to 32C would significantly alter the viscosity and/or the stiffness of the walls and thereby contribute to a modified distensibility of the arterial tree during hypothermia. Elastic and viscous constants were determined using helical strips quick-stretched (<5% of initial strip length, stretch interval 0.02 sec.) in a physiological salt solution free of added $Ca^{++}$. The femoral arterial walls had a viscosity increase from 1.55 to 3.38 X $10^5$ poise/cm ($p<0.01$). Moreover, the viscous force needed to stretch the walls increased from 9.8 to 13.8 X $10^5$ dyn/cm$^3$, ($p<0.01$). With this tissue, however, there was almost no change in stiffness 9.1 to 9.0 X $10^6$ dyn/cm$^2$ ($p>0.05$). Likewise, the abdominal aortic strips had major increases in viscosity when cooled (0.57 to 1.24 X $10^5$ poise/cm, $p<0.01$), but did not significantly alter the needed viscous force (0.86 to 0.91 X $10^6$ dyn/cm$^3$, $p>0.1$). In addition, the abdominal aortae had minor increases in stiffness when cooled that were statistically insignificant (6.53 to 6.94 X $10^6$ dyn/cm$^2$, $p>0.05$). Thus, a modest cooling appears to alter some of the viscoelastic properties of aortic and femoral artery walls that would in turn modify arterial capacitance.

16.7

TEMPERATURE REGULATION AGAINST COLD DURING G TUM-MO YOGA MEDITATION. Ralph F. Goldman and Herbert Benson*. Multi-Tech Corp., Natick, MA 01760 and Beth Israel Hospital & Harvard Medical School, Boston, MA 02215

Monks, studied in India, elevated finger/toe temperatures by >8°C during g Tum-mo meditation in cold conditions (Nature 295: 234, 1982). One, brought to the U.S. for $T_{re}$, Ts and metabolic (M) measurements in a climatic chamber, spent >10 years practicing g Tum-mo daily in isolation in an unheated hut at >2000m. One day after deplaning, two days prior to test, he was familiarized with all procedures, given a nose clip and mouthpiece with which to practice meditation. A Cu manikin was dressed in monk's garb; its insulation measured 1.6 clo. On test day, S was instrumented in chamber (thermistors) for on-line 3 point Ts, T finger and $T_{re}$ (10 cm), and seated for 30' baseline (Electrochem $O_2$/LB-2 $CO_2$ of Tissot sample analysis) at 9°C, 67% RH, 40 cm/s air motion. Baseline M=78W; $T_{re}$= 37.8; $\bar{T}_s$=30.2. Moving to Lotus position on mat on floor, he attempted to initiate Tum-mo but could not; M ↑ (to 95, to 110, to 175W); $T_{re}$ ↓ to 36.0C and $\bar{T}_s$ ↓ to 29 ± 0.5, with frank shivering. Chamber warmed to 15.5C and meditation initiated (M at 80W, $T_{re}$=36.1, $\bar{T}_s$=32.7). $T_A$ then lowered toward 10°C; M ↑ (80-94-100-112W), $T_{re}$ ↑ 36.3-36.5, $\bar{T}_s$ ↓ 31.5, with gooseflesh and frank shivering again, so exposure ended. S reported noseclip interfered with meditation. Unlike his response in India, Tfinger=18 ± 1°C throughout. We plan to measure M of Tum-mo meditation in cold in India next.

16.8

**EFFECTS OF ATROPINE ON THERMOREGULATION IN HEAT-STRESSED PATAS MONKEYS.** **Eleni Avlonitou* and Reynaldo S. Elizondo. Indiana University School of Medicine, Physiology Section, Medical Sciences Program, Bloomington, IN 47405**

**The effects of a single intramuscular atropine injection (.03 mg/kg) on the thermoregulatory effector responses of five unanesthetized Erythrocebus patas monkeys was investigated at ambient temperatures ($T_a$) of 25° and 35°C. Oxygen consumption, $CO_2$ production, mean weighted skin temperature ($\bar{T}_{sk}$), rectal temperature ($T_{re}$), respiratory evaporative water loss, total evaporative water loss and heart rate (HR) were measured continuously for 0.5 hour after equilibration at each $T_a$ and for an hour following the atropine administration. Atropine significantly decreased sweating by aproximately 32% and 50% at 25° and 35°C, respectively. Reduction of sweating resulted in significantly higher $T_{re}$ ($P<.01$) and $T_b$ ($P<.001$) at each $T_a$. HR was also significantly elevated ($P<.001$) by atropine at both $T_a$. The net heat load associated with the inhibited sweating caused by atropine was more pronounced at 35°C, however, it was partially compensated for by enhanced peripheral blood flow as indicated by significantly higher values for whole body conductance ($P<.05$) and $\bar{T}_{sk}$ ($P<.001$). These results, indicate that the thermoregulatory effects of atropine on nonhuman primates, are similar to those reported for man. It is concluded that the patas monkey can be an excellent model to evaluate the effects of neuroactive agents on thermoregulatory and probably other physiological functions under controlled experimental conditions which are difficult, if not impossible, to perform on humans.** **(Supported in part by USAF Contract F33615-83-D-0603).**

16.9

**THERMOREGULATION IN CERCOPITHECUS NEGLECTUS** **Rhoda Reddix-Cheri* and Reynaldo S. Elizondo. Indiana Univ. Sch. of Med. Physiology Section, Med. Sci. Prog., Bloomington, IN 47405**

**A thermal balance study was performed on four male unanesthetized De Brazza's Cercopithecus neglectus monkeys. Metabolic rate, mean skin temperature ($T_{sk}$), rectal temperature ($T_{re}$), respiratory evaporative water loss ($E_{resp}$) and total evaporative water loss ($E_{tot}$) were measured over a 30 minute interval at ambient temperatures of 15°C, 25°C, 30°C, 35°C, and 38°C in two adult De Brazza's monkeys. The same measurements were performed on two immature De Brazza's monkeys at ambient temperatures of 15°C, 25°C and 30°C. The adult De Brazza's maintained $T_{re}$ between 38.6°C and 39.6°C as the ambient temperature ($T_a$) increased. $E_{resp}$ was relatively constant. The immature De Brazza's could not maintain $T_{re}$ below 40.3°C at $T_a$ greater than 30°C and $E_{resp}$ increased from 6.4 W/m$^2$ at 15°C to 10.3 W/m$^2$ at 30°C. The metabolic rate was significantly higher in the immature De Brazza's (77.6 W/m$^2$-73.88 W/m$^2$) than in the adult (57.2 W/m$^2$-36.2 W/m$^2$). In both groups, the $T_{sk}$ increased with increasing ambient temperatures. $E_{tot}$ increased in the adult from 2.8 W/m$^2$ at 15°C to 46.4 W/m$^2$ at 38°C and in the immature De Brazza's from 2.8 W/m$^2$ at 15°C to 15.4 W/m$^2$ at 30°C. Sweat rate at the same $T_a$ was less in the immature monkey than in the adult. The sweat rate in the adults at 38°C (46.4 W/m$^2$), however, was significantly less than that in Erythrocebus patas (76 W/m$^2$) at the same temperature.** **(Supported in part by PHS grant GM 10595).**

16.10

CIRCULATORY ADJUSTMENTS TO THERMAL STRESS FOLLOWING CELIAC GANGLIONECTOMY IN THE RAT. K.C. Kregel*, P.T. Wall*, and C.V. Gisolfi. University of Iowa, Iowa City, IA 52242.

Previous findings have demonstrated that thermal tolerance of heat exposed rats depends on blood pressure maintenance. Hypotension associated with prolonged heating is in part attributed to a reduced splanchnic vasoconstriction at high core temperatures (Tc) (Fed.Proc. 45:1017,1986). The purpose of this study was to determine if celiac ganglionectomy (CGX) would further compromise thermal tolerance by reducing vascular resistance. Sprague-Dawley rats (270-320 g) were instrumented with (a) carotid artery and jugular vein catheters, and (b) pulsed Doppler flow probes on the left renal (LRA), superior mesenteric (SMA), and distal caudal (DCA) arteries. Under chloralose anesthesia, animals were exposed to 40°C until mean arterial blood pressure (MABP) declined to 60 mmHg. Blood flow in kHz Doppler shift, Tc, and MABP were measured. In control (C) animals (n=11), maximal % change ($\bar{x}$±SEM) in SMA, LRA, and DCA resistances, tolerance time, and final Tc were 112.8±22.8%, 379.0±94.9%, -86.0±2.7%, 90.6±33.7 min, and 43.5±0.1°C, respectively. Corresponding values in animals with CGX (n=7) were 5.0±6.2%, 81.2±27.5%, -75.5±4.2%, 69.6±3.8 min, and 42.8±0.2°C, respectively. Thus, CGX reduced the increase in SMA and LRA resistance observed during heating. Moreover, tolerance time decreased and Tc at a MABP of 60 mmHg was reduced. These data indicate that thermal tolerance is in part dependent on an intact innervation of renal and splanchnic beds. (Supported by NIH Grants AM-34986 and HL-32731.)

16.11

CIRCULATORY RESPONSES TO HYPERTHERMIA IN THE ANESTHETIZED RAT. P.C. Szlyk, I.V. Sils*, J.D. Ferguson*, and R.W. Hubbard. USARIEM, Natick, MA 01760-5007.

The circulatory responses to hyperthermia are not well documented since prompt treatment precludes data collection in human heatstroke victims. The present study examined the effects of hyperthermia (Tambient,Ta=42°C) on circulatory function in 11 anesthetized male Sprague-Dawley rats (528±3g). When Ta was raised from 22° to 42°C, rectal temperature (Tre) increased linearly from 37.0±.1°C to 43.6±.07°C at death. Heart rate (HR) remained relatively unchanged until Tre=39°C, then rose 60% to reach a peak at Tre=42.9°C before abruptly falling. Following an initial drop (8%), blood pressure (BP) increased 66% to attain a max value at Tre=41.9°C before again falling. Foot temperature (Tfoot) increased linearly with increasing Tre until dropping precipitously when Tre=42.9°C, whereas increases in Tskin at 4 other sites paralleled the rise in Tre. At Tre=41.8°C, cardiac output ($\dot{Q}t$) was elevated 124% by increases in stroke volume (SV) (62%) and HR (39%). Concurrent with the decline in HR and Tfoot was a 46% reduction in $\dot{Q}t$ at Tre=43.3°C which was primarily due to a decrease in SV (49%). Death ensued 14±1 min after the drop in HR and Tfoot and 103±3min after the start of increased Ta. Results show that elevated HR maintained $\dot{Q}t$ at high Tre and that the abrupt fall in HR and Tfoot are indicative of ensuing cardiac failure and death in the hyperthermic rat.

16.12

COMPARISON OF CORNEAL TEMPERATURE CHANGES ASSOCIATED WITH MAGNETIC RESONANCE IMAGING AT SPECIFIC ABSORPTION RATES BELOW AND ABOVE 0.4 W/KG. Frank G. Shellock and John V. Crues.* Cedars-Sinai Medical Center, Los Angeles, CA 90048.

Tissue heating occurs during magnetic resonance imaging (MRI), primarily as a result of exposure to radiofrequency (RF) radiation. The upper limit recommended for RF power deposition is a whole body averaged specific absorption rate (SAR) of 0.4 W/kg. Since the eye is particularly susceptible to heat damage, we investigated the temperature changes associated with MRI at estimated whole body averaged SARs below and above 0.4 W/kg. MRI was performed with a 1.5 Tesla system (Signa MR System, GE Company). Corneal temperatures (Tcor) were measured immediately before and after clinical MRI procedures. Data was analyzed as follows: Group I (N=50) - head MRI, SAR 0.05 to 0.07 W/kg; Group II (N=37) - body MRI, SAR 0.10 to 0.40 W/kg; Group III (N=47) - body MRI, SAR 0.50 to 1.30 W/kg.

| | Pre MRI Tcor | Post MRI Tcor |
|---|---|---|
| Group I | 32.7±0.7 | 33.1±0.6* |
| Group II | 32.6±0.6 | 33.0±0.6* |
| Group III | 32.5±0.7 | 33.0±0.6* |

(values are mean±SD, *$p<0.05$ pre compared to post MRI)
Changes in Tcor were not dependent on the location of the RF power deposition (i.e., head vs body MRI) nor the absolute whole body averaged SAR. Also, it should be noted that the elevations in Tcor were well below the threshold for producing heat damage.

16.13

SKIN WETTING (SW) REDUCES CORE TEMPERATURE (T) IN EXERCISING SWINE: M.D. McKirnan*, C.G. Gray*, R.J. Giamela*, M.J. Buono* and C.M. Bloor; U.C.S.D. School of Medicine and Naval Health Research Center, San Diego, California 92093.

Swine have been a valuable model for studies of exercise and cardiovascular regulation. We have used miniature swine for exercise studies lasting 5 hours at 65% $\dot{V}O2$ MAX. These studies were possible by shaving the body hair and frequent SW while a fan was blowing on the pig. We have also noted a pronounced skin erythema associated with increases in T. In contrast, recent data indicated that a minimal increase in skin blood flow (SBF) occurred during exercise, even when T was markedly elevated. To further examine evaporative heat loss secondary to increases in SBF, 4 pigs were exercised in a neutral environment at 65% $\dot{V}O2$ MAX under conditions of control unsprayed (C) or sprayed with water every 2 min (SPRAY). The rate of rise in T for SPRAY (.04°C/min) was significantly less ($p<.01$) than in C(.11°C/min). All C runs resulted in T > 41.4°C within 30 min of exercise, and 2 runs were terminated before 25 min. SPRAY runs were completed with a mean final T of 40.4°C. Our observations indicate that elevated SBF and SW results in greater evaporative heat loss and SW can be used to maintain lower T during exercise in swine.

Supported by funds from the U.S. Army Nutrition Task Force.

16.14

**THE EFFECT OF E. COLI LIPOPOLYSACCHARIDE INDUCED FEVER ON THE PERMEABILITY OF THE BLOOD-BRAIN BARRIER.** **Andrew N. Gustafson* and Reynaldo S. Elizondo. Indiana Univ. Sch. of Med., Physiology Section, Medical Sciences Program, Bloomington, IN 47405**

**Environmental hyperthermia and E. coli infection have both been implicated as conditions which increase blood-brain barrier (BBB) permeability. Lipopolysaccharide, a component of the E. coli cell wall has been shown to produce a regulated fever in rats. BBB permeability to $^{14}$C-sucrose (MW, 340 daltons) and $^{3}$H-dextran (MW, 70,000 daltons) was determined in afebrile and febrile rats by calculating the permeability-surface area product (PA) for several brain regions. Rectal temperature was monitored continuously throughout the course of the experiment. PA ($X10^{6}$, $S^{-1}$) values for afebrile rats were calculated for the cortex, cerebellum, medulla, and hypothalamic regions and averaged 6.42, 6.39, 5.38, and 5.60 for $^{14}$C-sucrose. The corresponding PA values for $^{3}$H-dextran were 0.94, 1.12, 0.94, and 1.02, respectively. E. coli lipopolysaccharide injected intravenously (50 ug/kg) produced a significant fever averaging 1.1°C. PA values for febrile rats were not significantly different from afebrile rats. The results indicate that lipopolysaccharide at a dose which produces fever does not alter BBB permeability in the rat, and is consistent with the hypothesis that the BBB is maintained during a regulated febrile state.** **(Supported in part by PHS SO7 RR 7031H).**

16.15

MODULATING EFFECT OF BODY TEMPERATURE ON THE TOXIC RESPONSE PRODUCED BY THE PESTICIDE CHLORDIMEFORM IN RATS, W.P. Watkinson*, J.W. Highfill*, and C.J. Gordon, MD-74C; E.B.D.; H.E.R.L.; U.S. Environ. Prot. Agency; R.T.P., N.C. 27711.

Previous studies from this laboratory have demonstrated significant deficits in cardiovascular function in rats exposed to the pesticide chlordimeform (CDM) when body core temperature ($T_{CO}$) was maintained at 37°C. To investigate the role of $T_{CO}$ on CDM toxicity, similar experiments were conducted over a range of $T_{CO}$'s. Adult rats (N=30) were anesthetized with sodium pentobarbital (35 mg/kg) and assigned to one of six equal groups. Groups were paired and $T_{CO}$ was maintained in the rats in each of the respective group pairs at one of three levels (37°, 35°, and 33°C). Heart rate (HR) was monitored throughout the experimental procedure. Rats in one group at each temperature level ($T_{37}$, $T_{35}$, and $T_{33}$) were injected intraperitoneally with 60 mg/kg of CDM. Animals in the corresponding groups ($C_{37}$, $C_{35}$, and $C_{33}$) received a volume-matched injection of normal saline vehicle and served as time-paired controls. There was a significant decrease in HR in all CDM-treated groups when compared to the control group animals. The magnitude of the cardiac effect was attenuated in the $T_{35}$ group. Similarly, lethality rates (# deaths/# total) for the $T_{37}$, $T_{35}$, and $T_{33}$ groups were 2/5, 0/5, and 3/5, respectively; there were no deaths among the control group animals. From these and previous data from this laboratory, we conclude there may be a beneficial effect of hypothermia in rats which is maximal around 35°C.

16.16

REGULATED HYPOTHERMIA: A POSSIBLE MODE OF PROTECTION AGAINST ACUTE TOXIC INSULT, C.J. Gordon and W.P. Watkinson*, MD-74C; E.B.D.; H.E.R.L.; U.S. Environ. Prot. Agency; R.T.P., N.C. 27711.

We propose that regulated hypothermia (Life Sci., 32:1285-1295, 1983) may constitute a general mechanism whereby survivability is improved following an acute toxic insult. In one series of experiments, mice were injected intraperitoneally (i.p.) with single, nonlethal doses of toxic compounds, including triethyltin, sulfolane (S), chlordimeform (CDM), $NiCl_2$, $CdCl_2$, and lead acetate. The animals were immediately placed in a temperature gradient and were permitted to select their preferred ambient temperature ($T_a$). In a second series of experiments, naive mice were injected i.p. with the above compounds and placed in a temperature-controlled environmental chamber. Animals were tested at several $T_a$'s, including the previously determined preferred $T_a$, over the range of 20-35°C. Body temperature was recorded and metabolic rate was calculated at 60 min. In general, all toxic compounds led to reductions in body temperature and metabolic rate; this effect was potentiated at the lower $T_a$'s. Treated mice placed in the temperature gradient selected a cooler $T_a$ than the controls; in some cases, this preferred $T_a$ was as much as 10°C below the control group's preferred $T_a$. Percent mortality of mice treated with $LD_{50}$ doses of S and CDM was directly correlated with $T_a$. Thus, by lowering body temperature through behavioral and autonomic mechanisms, mice appear to increase their chance of survival following exposure to toxic agents.

16.17

EFFECT OF ETHANOL ON TEMPERATURE SELECTION IN THE GOLDFISH, CARASSIUS AURATUS. C.S. O'Connor*, L.I. Crawshaw and J.C. Crabbe*. Portland State University, Portland, OR 97207

The effect of ethanol on thermoregulation was studied in the goldfish. Ethanol was administered to 10 to 15 g fish in the water of a temperature gradient. The fish responded to ethanol by selecting temperatures about 2C below those selected by controls in water. The dose response curve was very steep between 0.5% (v/v) ethanol (no response) and 0.7% (significant lowering of selected temperature in treated fish). At concentrations above 0.7%, the magnitude of the effect did not appear to increase with increasing concentrations of ethanol. Fish were exposed to concentrations as high as 1.7%, at which most experimental fish lost their ability to swim upright. Experiments exposing fish to 1.0% ethanol for up to 3 hr showed that the effect remained stable for this period of time. We conclude that ethanol produces a prompt, reproducible depression of selected temperature in the goldfish. Because the temperature at which fish regulate is controlled by the central nervous system and is not altered by action on peripheral effector systems, it appears that ethanol causes hypothermia in goldfish by directly acting to lower the set point.

(This research is partially supported by Grant AM 34736 from the National Institutes of Health.)

16.18

OPIOID AGONIST ACTIVITY OF AN ISOLATED ALBUMIN FRACTION FROM THE PLASMA OF HIBERNATING WOODCHUCKS. John R. Welborn* & Peter R. Oeltgen*, Lexington VA Medical Center & Univ of KY College of Medicine, Lexington, KY 40511, & Wilma A. Spurrier, Stritch School of Medicine, Loyola University, Maywood, IL 60153.

We have successfully utilized the mouse vas deferens (M.v.d.) assay of Henderson, et. al., Br. J. Pharmac. 57: 551, (1976) to demonstrate that an affinity chromatography albumin fraction derived from the plasma of hibernating woodchucks has opioid agonist activity which can be partially blocked by 250 nM naloxone. In this rapid in vitro assay, we utilized vas deferens from ICR Swiss Albino mice (Simonson Laboratories), weighing 35-45g. The dissected vas deferens were placed in a 5 ml organ bath containing Krebs solution as specified by Henderson, et. al. (1976) and gassed with 95% $O_2$ / 5% $CO_2$ at 37°C. The vas deferens were stimulated by 1 m sec rectangular pulses of supra maximal voltage at 0.1 Hz for 20 minutes prior to treatments with varying concentrations (20-200 µg/ml) of albumin fractions derived from the plasma of hibernating and summer-active woodchucks. Dose response experiments indicated that maximal twitch inhibition of 37% could be achieved with the 200 µg/ml albumin fraction from hibernating woodchucks while a similar concentration of albumin fraction from summer-active woodchucks resulted in a maximal twitch inhibition of 9%. We plan to utilize the M.v.d. assay to monitor the opioid activity of plasma fractions of hibernators as they are further purified. Supported by the Veterans Administration.

16.19

SEASONAL VARIATIONS IN THE RATIO OF SERUM UREA TO CREATININE (U/C) IN BLACK BEARS. E.R. Ensrud*, R.A. Nelson, G. Alt*, T. Beck*, G. Matula*, and L. Rogers*. Carle Foundation and Univ. of Illinois, Urbana, IL 61801.

A previous study showed that U/C varies with bear behavior. The investigation of this relationship was expanded to include bear populations from several locales in the U.S. Over a period of 5 years, 250 serum samples were collected from Colorado, Maine, Minnesota, and Pennsylvania. Field serum samples were frozen (for transport and storage), thawed, and assayed for urea and creatinine. Results showed that U/C values were within normal mammalian limits (>20) in summer, declined in late summer and early fall prior to denning, reached their nadir (<10) in winter during denning, and returned to normal values in spring when activity resumed. However, a number of bears reached their nadir prior to denning. It was concluded that seasonal variations in U/C occur in large populations of bears, and are indicative of annual changes in metabolism. Bears which reached their nadir prior to denning suggest the biochemical state of hibernation is independent of denning behavior.

16.20

DO LOW LEVELS OF CONADAL HORMONES DURING REGRESSION OF REPRODUCTIVE ORGANS STIMULATE THERMOREGULATORY CHANGES FOR WINTER? Carol F. Feist*, Dale D. Feist and G. Robert Lynch. Univ. of Alaska, Fairbanks, AK 99775 and Wesleyan Univ., Middletown, CT 06457

White-footed mice (Peromyscus leucopus) were exposed to long day (L=16h light:8h dark) and warm (W=25°C) or cold (C=5°C) or short day (S=9h:15h) and warm or cold. Each of these four groups was subdivided into 1) controls: sham castrated + sham implanted, 2) castrated + sham implanted and 3) castrated + implanted with testosterone (T). Mice were tested for nonshivering thermogenesis (NST) at 4, 8 and 12 wk and examined for reproductive and pelt condition after 12 wk. Cold increased NST in all groups by 4 wk. In controls, short day decreased testes weight and serum T, caused molt to winter pelt, but did not increase NST. Castration, with no detectable serum T, facilitated molt to winter pelt in SW, LW and LC mice and reduced cold enhanced NST in L mice. High serum T from implants prevented short day induced molt to winter pelt and reduced cold enhanced NST in L mice. The results suggest 1) a linkage between regression of gonads and molt of pelage in fall but 2) no linkage for enhancement of NST which is stimulated by cold via a separate pathway, 3) some factor in the testes, other than low T, may be necessary for normal cold enhancement of NST, and 4) a linkage between high T and reduction of NST as during recrudescence of gonads in spring.

## RENIN-ANGIOTENSIN

17.1

ADVERSE EFFECTS OF ANGIOTENSIN & CALMODULIN ON THE VASCULAR SMOOTH MUSCLE OF THE COLD PRESERVED KIDNEY. J. Prives*, D. Anaise*, B. Lane, and F.T. Rapaport* (SPON: Lorne Mendell ). SUNY at Stony Brook, Stony Brook, N.Y. 11794-8192

Reperfusion injury (RI) is increasingly recognized as a key factor in the development of post-transplant acute tubular necrosis. Previous studies have shown that addition of the calmodulin (Cam) inhibitor Trifluoperazine (TFP) to Collins' flush solution protects the cortical microcirculatory integrity and dramatically improve renal viability after transplantation. The present report describes the protective effect(s) of TFP in the course of reperfusion injury. Ten mongrel dogs underwent bilateral nephrectomy; in each instance, the left kidney was flushed immediately with Collins' solution (C), and the right kidney was flushed with the same solution containing TFP, 5 mg/ml. After 48 and 72 hours of preservation, each kidney was transplanted to the femoral vessels of another dog. The renal blood flow (RBF) immediatelyafter reperfusion was 2.2 cc/g/min and 1.7 cc/g/min in the left and right kidneys, respectively and was similar to the measurements prior to nephrectomy. After 15 minutes of reperfusion, there was a sharp decrease in RBF in the C flushed kidneys which persisted after 60 minutes of reperfusion (0.29 cc/g/min). In contrast, there was only a mild decrease in RBF in the TFP flushed kidneys (1.27 cc/g/min). Administration of 1.25 mg/kg of Captopril, an Angiotensin (A) converting enzyme inhibitor, resulted in dramatic amelioration of RI. Parallel studies in cultured muscle have shown that TFP blocked Cam driven cytoskeletal changes rendering the muscle insensitive to A stimulation thus preventing RI.

17.2

RENIN SECRETION IN INTACT DOGS FOLLOWING INCUBATION OF EPINEPHRINE IN BLOOD IN VIVO. Michael D. Johnson. West Virginia University, Morgantown, WV 26506.

Previous experiments have demonstrated that epinephrine (E)-induced renin secretion is not due to a direct intrarenal effect of E. The present experiments were designed to evaluate the hypothesis that E-induced renin secretion is initiated by a change in blood composition, independent of passage of the blood through any organ. Accordingly, the left kidneys of anesthetized dogs were pump-perfused with femoral arterial blood via an extracorporeal circuit. The circuit consisted of large-bore silastic tubing (157 ml volume) with an infusion port and a mixing chamber near the femoral arterial origin, and a blood sampling and pressure-monitoring site near the renal artery. A roller pump was used to maintain renal perfusion pressure approximately equal to femoral arterial pressure, and renal blood flow was measured with an electromagnetic flowmeter. Transit time (of a dye) in the extracorporeal circuit was approximately 40 seconds. Intravenous infusion of E at 25 $ng \cdot kg^{-1} \cdot min^{-1}$ increased renin secretion significantly. However, infusion of E into the extracorporeal circuit at a rate of 5 $ng \cdot kg^{-1} \cdot min^{-1}$ did not alter renin secretion, even though measured renal perfusate E concentration was higher than during intravenous E infusion. The data do not support the hypothesis that E-induced renin secretion is initiated by a direct effect of epinephrine on blood itself, independent of the passage of blood through any organ. (Supported by NIH Grant HL-25555.)

17.3

NATRIURESIS DOES NOT CAUSE THE ENHANCED SALT APPETITE OF MULTI-DEPLETED RATS. R.R. Sakai*, S. Frankmann*& A.N. Epstein, Univ. of Pennsylvania & Monell Chemical Center, Phila. Pa. 19104

Multiple sodium depletions produce an essentially lifelong enhancement of salt appetite that is greater in females than in male rats. That is, animals that are expressing a salt appetite after their second (and subsequent) Na depletion (SC furosemide and overnight removal of ambient Na) drink 3% NaCl sooner (0 latency) and in greater volume (10.5 ± 1.3 vs 6.8 ± 0.5 ml). The enhancement is expressed as long as 3 months after the 1st depletion. Persistent natriuresis is not the cause of the enhancement. Urine was collected from adult rats of both sexes (5-6/group) that had either never been depleted of Na (depletion-virgins) or had been depleted 4 times at weekly intervals in the month before collection began (multi-depleted) and had expressed enhanced appetite after their 2nd depletion. The collections were made while the animals ate Na deficient food for 24 hrs. Na excretion was: depletion-virgin females, 1.38 ± 0.08 mEq at 126.7 ± 12 mEq/L vs 1.24 ± 0.12 mEq at 102.8 ± 14.4 mEq/L in the multi-depleted females: depletion-virgin males, 0.70 ± 0.18 mEq at 53 ± 16.9 mEq/L vs 0.50 ± 0.21 mEq at 47.5 ± 20.6 mEq/L in multi-depleted males. Thus, multi-depleted rats conserve Na as effectively as depletion-virgin rats. This strengthens our suggestion that the enhanced salt appetite of multi-depleted rats is the result of a lifelong up-regulation of the brain's receptor systems for the synergistic action of angiotensin and aldosterone. Supported by: NS 03469, MacArthur Foundation & National Dairy Foundation.

17.4

CHANGES IN PLASMA ANG AND ALDO DO NOT ACCOUNT FOR THE ENHANCED SALT APPETITE OF THE MULTI-DEPLETED RAT. A.N. Epstein, R.R. Sakai*, & B. Stamoutsos*, Univ. of Penn, Phila. Pa. 19104

The salt appetite of Na depletion is enhanced in the rat by a prior depletion. The enhancement occurs abruptly and completely after the 2nd depletion and is expressed by virtual disappearance of latency and by near doubling of volume of 3% NaCl consumed. We now report that changes in plasma angiotensin II (ANG) and aldosterone (ALDO) do not account for the enhanced salt intake. Male rats were sodium depleted (10 mg/rat furosemide, overnight removal of ambient sodium) and were either sacrificed for trunk blood the next AM or were given access to 3% NaCl. Depletion was repeated in the latter. Groups of them were sacrificed just after their 2nd, 3rd and 4th depletions. ALDO (RIA, Diagnostic Prod.) rose after the 1st and did not increase further until the 4th depletion (see: Soc. Neurosci. Abstr. 12, 1986). ANG II (RIA, Iowa antibody) rose sharply after the 1st depletion and did not increase further (non-depleted (N=13): 143 pg/ml, 1st dep (N=11): 1807 pg/ml, 2nd dep (N=4): 1205 pg/ml, 3rd dep (N=6): 1533 pg/ml, 4th dep (N=6): 1425 pg/ml). Plasma ANG and ALDO are both markedly increased by Na depletion but their subsequent changes with successive depletions does not match the abrupt and complete enhancement of salt appetite that occurs after a second depletion. This supports our suggestion that, when they are first elevated, these hormones organize long-lasting changes in the brain that increase the animal's avidity for salty substances. Supported by NS 03469.

17.5

RENIN IN UTERINE LUMINAL FLUID FLUSHINGS. N. Emmett*, E. Archibold*, L. Dukes*, W. Pryor* and J. Edwards* (SPON: R. Sridaran). Dept. of Physiology, Morehouse School of Medicine and Dept. of Biology, Morehouse College, Atlanta, GA 30310.

Renin is an endopeptidase that specifically cleaves angiotensinogen to produce angiotensin I. Although the primary site of renin synthesis is the kidney, renin is also produced in sufficiently significant quantities by other tissues, such as the uterus. We have examined purified renin from nonpregnant and pregnant rabbit uterus using immunochemical techniques. Consistent with previous findings, the results indicated the presence of renin activity and showed significant changes in renin concentration in the two sources. Proteins in the luminal flushings were also analyzed for the presence of renin by analytical gel electrophoresis and immunoblot examinations according to published procedures. The results from these studies demonstrated the presence of renin and support the hypothesis that endometrial cells could serve as a cellular source of renin released into the luminal flushings. In this regard, we have isolated mRNA from polysomes obtained from these extracts using immunoabsorption with renin-specific antibodies. Translation of renin from this purified poly (A+ RNA) preparation would suggest that the uterus is a site for renin production. (Supported by NIH Grant 5-S06 RR 08006-15 and NIH IS-11RR02 770-01).

## ACID-BASE AND RENAL SOLUTE TRANSPORT

18.1

GLUCOCORTICOIDS REGULATE RENAL AMMONIAGENESIS IN ACIDOSIS. Tomas C. Welbourne. LSUMC, Shreveport, LA 71130

The role of glucocorticoids in regulating renal ammoniagenesis was assessed in adrenalectomized, ADX, sham treated, MA, and ADX plus triamcinolone supplemented, 50 mg/100g/day, ADX+S, male Sprague-Dawley rats. Adx rats were maintained on 0.15 M NaCl for 10 days following Adx. Metabolic acidosis was induced by administering 0.6% $NH_4Cl$ and 5% Dextrose in 0.15 M NaCl over 3 days. All 3 groups consumed similar amounts of acid. However, 24 hour ammonium excretion, UV-$NH_4^+$, was markedly different (in μmole/100g/day): nonacidotic=107±7, MA=1691±318, ADX+MA=718±82 and ADX+MA+S=2813±476. ADX rats excreted $NH_4^+$ at a rate of only 42 per cent of the MA; triamcinolone restored the UV-$NH_4^+$. The quantitative significance of the UV-$NH_4^+$ results was assessed by measuring the sum of renal venous and UV-$NH_4^+$ in vivo with the following results in nmole/min/100g: nonacidotic=504±90, MA=2068±139, ADX+MA=863±104 and ADX+MA+S=2813±476. These results show that ADX rats respond much less to the acid load when assessed on the basis of true ammonia production, 1.7 fold greater than nonacidotic, rather than the 6.7 fold suggested by UV-$NH_4^+$ data. Furthermore, triamcinolone returned and actually elevated ammonia production 1.4 fold above the intact MA group. The cellular mechanism underlying this glucocorticoid effect is presently under investigation.

18.2

EXPERIMENTAL CPR: EFFECTS OF SODIUM BICARBONATE THERAPY ($NaHCO_3$). Hanumant G. Deshmukh*, Chalapathirao Gudipati*, Max H. Weil, Joe Bisera*, and Eric C. Rackow. The Chicago Medical School, North Chicago, IL 60064

$NaHCO_3$ is administered during CPR to correct metabolic acidosis with the assumption that it improves resuscitability. In a porcine model of CPR, $NaHCO_3$ 1.5 mEq/kg (0.23 mEq/ml) or equal volume of NaCl placebo was administered 8 mins after induction of VF in 16 animals. The central aortic (ao), coronary venous (gcv) blood gases and lactic acid (L) were measured 1 min before (A) and 3 min after (B) drug infusion.

| | | $NaHCO_3$ (8) | | | Saline (8) | | | p |
|---|---|---|---|---|---|---|---|---|
| | | A | B | Δ | A | B | Δ | |
| ao | pH units | 7.44 | 7.50 | +0.17 | 7.45 | 7.37 | -0.08 | 0.001 |
| | $PCO_2$ mmHg | 39 | 52 | +12 | 39 | 39 | +0.2 | 0.01 |
| | $HCO_3$ mEq/L | 26 | 38 | +12 | 25 | 22 | -4 | 0.001 |
| | L mmol/L | 2.1 | 3.3 | +1.3 | 2.0 | 2.7 | +0.7 | 0.01 |
| gcv | pH units | 6.83 | 7.11 | +0.29 | 6.89 | 6.98 | +0.07 | 0.001 |
| | $PCO_2$ mmHg | 137 | 125 | -12 | 125 | 105 | -19 | NS |
| | $HCO_3$ mEq/L | 22 | 38 | +16 | 23 | 23 | -0.3 | 0.001 |
| | L mmol/L | 7.0 | 8.3 | +1.3 | 7.5 | 6.7 | -0.6 | NS |

Administration of $NaHCO_3$ produced significant alkalosis, hypercarbia and lactic acidemia in ao and alkalosis in gcv blood. Five $NaHCO_3$ and 6 placebo treated animals were successfully resuscitated. $NaHCO_3$ did not improve resuscitability. However, there were increases in ao $PCO_2$ and ao and gcv lactate associated with $NaHCO_3$ administration and these would be likely to decrease myocardial resuscitability.

18.3

ACID BASE DETERMINANTS OF RESUSCITABILITY DURING EXPERIMENTAL CARDIOPULMONARY RESUSCITATION (CPR). Chalapathirao Gudipati,* Max H. Weil, Hanumant G. Deshmukh,* Joe Bisera,* and Eric C. Rackow. The Chicago Medical School, North Chicago, IL 60064

Since substantial increases in the great cardiac vein (gcv) $PCO_2$, and comparatively lesser increases in lactic acid (L) were observed, we further investigated the extent to which increases in gcv $PCO_2$ affected resuscitability. In a previously described porcine model of CPR, 5 min after ventricular fibrillation (VF) was induced, conventional CPR including precordial compression and mechanical ventilation was performed for 8 min in 16 animals. Electrical conversion with DC countershock was then attempted. Central aortic (ao), gcv blood gases, and L were measured at 11 mins after onset of VF.

| | | R (11) | NR (5) | p |
|---|---|---|---|---|
| ao | pH, units | 7.43 | 7.47 | NS |
| | $PCO_2$, mmHg | 44.0 | 49.0 | NS |
| | L, mmol/L | 3.1 | 2.6 | NS |
| gcv | pH, units | 7.07 | 6.80 | <0.05 |
| | $PCO_2$, mmHg | 106.0 | 147.0 | <0.05 |
| | L, mmol/L | 7.3 | 8.9 | NS |

A disproportionate increase in gcv $PCO_2$ was observed. Arterial blood gases failed to reflect the striking myocardial respiratory acidosis. These findings suggest that the capability for resuscitation is decreased when gcv $PCO_2$ is increased.

18.4

THE KIDNEY'S ROLE IN ACID-BASE, ELECTROLYTE, AND LACTATE EXCRETION IN RESPONSE TO HIGH INTENSITY EXERCISE. R.S. McKelvie*, M.I. Lindinger*, G.J.F. Heigenhauser. McMaster Health Sciences Centre, Hamilton, Ontario, L8N 3Z5, Canada

Five healthy males performed four 30 sec. bouts of exercise, separated by four min of rest, on an isokinetic cycle ergometer. Arterial blood and urinary catheter samples were taken immediately post exercise and for 90 min into recovery. Inulin was continuously infused to measure GFR. Arterial plasma [Na+], [K+], and [Cl-] increased significantly ($p<0.05$) with exercise, [K+] was lower than control from 20 to 90 min of recovery. Plasma [La-] increased from 1.3± (SEM) 0.2 to 21.0±1.0 mmol/l. Reduction of renal Na+ and K+ clearance occurred respectively at 60-90 and 30-90 min of recovery. There were significant inverse linear relationships between urine [Cl-] and [La-] ($r=-0.84$) ([La-]=190 mmol/l; [Cl-]=6 mmol/l at 30 min recovery) and between urine strong ion difference (SID) and [H+] concentration ($r=-0.64$). A positive relationship existed between urine [La-] and [H+] ($r=0.72$). Renal La- clearance peaked (27.7±5.12 ml/min) and Cl- clearance reached a low (0.07±0.01 ml/min) at 30 min of recovery, both returning towards control throughout recovery. Only 1.7% of the total La- produced (768 mmol) was excreted in the urine demonstrating that the kidney plays a minor role in correcting the acute metabolic acid load. Furthermore La- is preferentially excreted by the kidney and Cl- is preferentially reabsorbed to prevent excessively large increases in urine [H+]. Supported by OHSF and MRC.

18.5

SYNTHETIC ATRIAL NATRIURETIC PEPTIDE (ANP) DECREASES DEEP NEPHRON PROXIMAL TUBULE SODIUM REABSORPTION. John A. Haas and F. G. Knox, Mayo Clinic and Foundation, Rochester, MN 55905

Micropuncture studies have demonstrated that ANP does not inhibit superficial proximal tubule sodium reabsorption. However, clearance studies have shown that the natriuretic effect of ANP is associated with an increase in urinary lithium excretion, a marker for whole kidney proximal sodium reabsorption. The present micropuncture study was performed to determine if ANP increases deep proximal sodium delivery. A comparison was made of fractional sodium delivery ($FD_{Na}$) to the superficial late proximal tubule, the descending limb of Henle's loop of juxtamedullary nephrons (Deep) and the papillary tip (Urine) in response to either ANP infusion, 4 µg/kg/hr, (n=9) or saline vehicle infusion (n=8). ANP infusion increased the urinary $FD_{Na}$ from 1.34±.71 to 3.78±.60%, $p<.001$. In response to ANP infusion, $FD_{Na}$ to the deep proximal tubule changed from 28.1±4.0 to 35.5±4.4%. In time control animals, $FD_{Na}$ was 30.9±3.6% before and 22.6±4.4 after vehicle infusion. Thus, a significant difference was observed between the change in $FD_{Na}$ after ANF infusion (Δ+7.2±4.7) as compared to control (Δ-8.3±4.1). (ANF infusion versus control, Δ15.5±6.3%, $p<.05$). No significant change in $FD_{Na}$ from the superficial proximal tubule was observed in either control or ANP-infused rats. In summary, sodium delivery to the point of micropuncture in the descending limb of Henle's loop of deep nephrons was increased, suggesting inhibition of sodium reabsorption by proximal tubules of deep nephrons. (Supported by HL14133)

18.6

DEVELOPMENT OF RENAL RESPONSE TO HIGH K INTAKE. Sidney Solomon, Susan Hathaway, and Phyllis Develin*. University of New Mexico, Department of Physiology, Albuquerque, NM, 87131.

Studies have been carried out on infant and mature rats to determine if pups can adapt to a high $K^+$ intake in the postnatal period. Metabolic studies of animals fed on high K diet and given KCl drinking water show that 21 day old pups can adapt as well as mature animals. Both groups increase fluid intake as compared to rats on a normal diet drinking tap water. The infants do not eat as much solid high K food as controls, while mature animals reach the same level of intake. Acetazolomide has comparable effects in both groups. Sulfate produces a greater increase in K excretion by young pups on a normal diet and produce quantitatively comparable changes in mature control and K adapted rats. In juveniles sulfate reduces GFR in adapted rats while urinary volume and K excretion are not as great as in control. It is concluded that infant rats can adapt to K intake at 21 days of age, that the distal nephron probably secretes K at this time and that any differences in renal function are probably a result of reduced GFR. Supported by grants from NSF #8215938 and NIH #7F32HL06686.

18.7

RAPID RESPONSE TO INTRAVENOUS POTASSIUM FORCING. David B. Young. Dept. of Physiol. and Biophys., Univ. Miss. Med. Center, Jackson, MS 39216-4505

Control of plasma K concentration in response to iv K forcings was analyzed in 5 conscious dogs using a system to measure continuously blood K activity and pH. The forcings were injections of 1.0 or 2.0 meq KCl over a 30 sec. period. While the dogs were maintained on a normal diet the initial plasma K averaged 4.33 ± .10 meq/l. The plasma K responses to the 1.0 and 2.0 meq forcings were 0.60 ± .03 and 1.13 ± .07 meq/l increases, respectively. In both cases the response to the increase in K returned plasma K to the initial level in 5 minutes. pH was unaffected. The responses were also analyzed in the same dogs after one week on diets with a high K content (200 meq/day) or a high Na content (200 meq/day). On the high K diet initial plasma K averaged 4.34 + .09 meq/l. The responses in plasma K to the 1.0 and 2.0 meq K challenges in the dogs on the high K diet were 0.68 ± .07 and 1.39 ± .08 meq/l increases. The initial plasma K in the dogs maintained on a high Na diet was 3.90 ± .06 meq/l. The responses to the K challenges were 0.70 ± .10 and 1.34 ± .18 meq/l. There were no significant differences among the responses to K challenges while the dogs were consuming the diets containing the different Na and K mixtures. These findings suggest that the systems which maintain long-term K regulation and respond to changes in K and Na intake do not affect the responses to rapid perturbations in plasma K. Supported by HL 21435.

18.8

EVIDENCE FROM RAT BIOASSAY FOR CIRCULATING KALIURETIC REGULATORY FACTORS OTHER THAN ALDOSTERONE AND PLASMA POTASSIUM. L. Rabinowitz, P.A. Tzendzalian, and H. Yamauchi. University of California, Davis, CA 95616.

Kaliuretic regulatory factors other than plasma K, aldosterone and the rates of Na and urine excretion were inferred in sheep (Am. J. Physiol. 247: F520-F526, 1984). To test for such factors in the rat we used as bioassay unanesthetized rats with a chronically implanted jugular vein catheter. They received brief (10-20 min) intravenous infusions of donor plasma or other fluids (5-15 ml). Urinary K excretion during one hour was the indicator of kaliuretic activity. Infusion of plasma from K loaded rats into assay rats that were not pretreated (I) or pretreated with mannitol diuresis (II and III) doubled K excretion compared to plasma from non-loaded rats (IV), Ringers solution iso-oncotic with bovine serum albumin (V), or saline without or with K (8 mM) (VI). K vs Na excretion (microeq in 1 hour) were respectively: I 360 vs 1230, II 256 vs 254, III 282 vs 319, IV 145 vs 118, V 121 vs 71, and VI 141 vs 502. The estimated maximum quantity of aldosterone in donor plasma was approximately 0.001 that required to produce an equivalent kaliuresis. These results suggest the presence of circulating, transmissible factor(s) in rat plasma that produce a rapid and large stimulation of K excretion in unanesthetized assay rats. These factors are not aldosterone or plasma K and they do not act through increasing the rate of urine flow or sodium excretion.

18.9

INHIBITION OF THE CALCIUM CASCADE IN RENAL ISCHEMIA. F.Greif*, D. Anaise*, L.Arbeit*, L.Frei*, H.S.Soroff* (SPON:L.C.Moore). SUNY at Stony Brook, Stony Brook, NY 11794-8191

The calcium-calmodulin (Ca-Cam) complex is a prime mediator of cell reactions leading to cellular necrosis. The rapid influx of Ca into the cytosol during ischemia exceeds the buffering capacity of the mitochondria, resulting in the activation of the Ca-Cam complex. This in turn causes activation of phospholipases, membrane breakdown, cytoskeleton damage, and adversely affects mitochondrial respiration. This deleterious cascade may potentially be interrupted at 3 distinct points 1.by reducing Ca influx. Using Verapamil (Verap) 2.by increasing mitochondrial capacity to sequester Ca, using Ethan-1-hydroxyl 1:1 disphosphonic acid (EHDP) 3.by inhibiting of the Ca-Cam complex Triflouperazine (TFP). The protective role of these Ca antagonists in ameliorating renal injury during prolonged ischemia was evaluated. 130 unilaterally nephrectomized Sprague Dawley rats underwent total occlusion of the renal artery for 90 minutes. They were assigned to 9 groups which received either .5 ml of saline preoperatively, or Verap, EHDP, or TFP at various doses. Survival rate of TFP, Verap, and EHDP pretreated rats was 90%, 87.5% and 60% respectively, in contrast only 33% of control rats survived. Dose response curves have established the optimal protective dose required. These data highlight the need for control of intracellular Ca during prolonged renal ischemia.

18.10

UNMASKING RHEOGENICITY OF GLUTAMATE COTRANSPORT: POSSIBLE MECHASNIMS. Erich Heinz, David L. Sommerfeld* and Rolf Kinne. MPI fuer Systemphysiologie, 4600 Dortmund, FRG

The $Na^+$-linked cotransport of glutamate into renal brush border membrane vesicles becomes (positive) rheogenic in the presence of an outward $K^+$-gradient. This unmasking of the rheogenicity can be explained in terms of a classical carrier model (including the Patlak-Laeuger gate mechanism) where the $K^+$ glutamate antiport shifts the rate-limiting transport step from the translocation of the (neutral) unloaded site to that of the (positive) substrate loaded one. Rheogenicity of the sodium-glutamate cotransport is also revealed by lowering the extravesicular pH, but under these conditions the net transport of glutamate is strikingly increased whereas the $K^+$-effect is reduced. In order to accomodate the latter observations the above model has to be expanded by including a pH-dependent transition between an alternating Patlak-Laeuger type gate mechanism and an open channel.

## NEUROBIOLOGY

19.1

THE EFFECT OF CROMOLYN SODIUM STABILIZATION OF MAST CELLS ON OCULAR RECURRENCE OF HSV LESIONS IN RABBITS. Fred Yates, M.S. Ysolina Centifanto, Ph.D., Delmar R. Caldwell, M.D., Dept. of Ophthalmology, Tulane University School of Medicine, New Orleans, LA.

Recurrence of HSV lesions in animals and man has long been associated with various forms of trauma (mechanical, thermal, chemical and electromagnetic) to either the initial infection site or to the ganglia and axons serving that site. Animal models have utilized all of these mechanisms in order to induce recurrences of HSV lesions in the skin and eye. In common with all non-neural manipulation models of recurrence are 1) physical damage to cells at the post-infective site and 2) probable degranulation of mast cells at or near the lesion site. Neural manipulation models may involve inflammatory mediator release as well. Cromolyn sodium acts principally at the level of the mast cell to stabilize membranes and prevent mediator release. The actual signal for initiation of recurrence is not known but may be involved with one or more mediators contained in mast cells. This study addresses the role of the mast cell in signalling recurrence by effectively eliminating it as a variable in the rabbit eye mode.

19.2

TETRAETHYLAMMONIUM CHLORIDE (TEAC): A NEW APPROACH TO THE TREATMENT OF HSV LESIONS. Ysolina Centifanto, Ph.D., Fred Yates, M.S., Delmar R. Caldwell, M.D., Dept. of Ophthalmology, Tulane University School of Medicine, New Orleans, LA.

The antiviral action of Tetraethylammonium chloride (TEAC) on dermal and ocular herpetic lesions was investigated. In the guinea pig model topical application of 5% TEAC ointment was found effective in reducing the number and duration of skin lesions and in minimizing scar formation. In the New Zealand white rabbit ocular model topical application of a 1% TEAC solution 3 x daily started 3 days after infection with HSV-1 McKrae strain significantly reduced the severity of ocular infection and prevented death due to encephalitis. The mouse ear model (Hill, J Gen Virol 39:21, 1978) was used to test the effect of TEAC on recurrent herpetic lesions. Preliminary data indicated that TEAC was effective in preventing recurrent lesions. The use of topical TEAC is a new approach to the treatment of HSV lesions.

19.3

EFFECT OF CAPSAICIN ON CHICK DORSAL ROOT GANGLION CELLS. Diana L. Kunze*, H. Dieter Lux, and Arthur M. Brown*. Baylor Col Med, Houston, TX and Max-Planck-Institut fur Psychiatrie, Martinsried, Germany.

The effect of capsaicin (CAPS) on the inward rectifying potassium channel in dorsal root ganglion cells from 10 day old chick embryo was examined using the patch clamp technique for whole cell and single channel recording. The inward rectifier was present in about half of the cells studied. Symmetrical isotonic KCl solutions were used most frequently to study the currents. They were blocked by extracellular Ba (100 $\mu$M) or Cs (1 mM). When CAPS was added to the bath ($10^{-8}$-$10^{-5}$M) inward currents were reduced as was the slope of the current voltage relation. The block was always incomplete even at concentrations as high as $10^{-5}$M. Single channel conductance in isotonic K was 25-35 pS and showed a square root dependence on $K_o$. There was no effect of CAPS on single channel amplitude in outside out patches. There was a decrease in the probability of opening as indicated by the presence of traces with no channel openings. Mean open times were unchanged. When CAPS was added to cells bathed in a normal extracellular solution containing 5 mM K the response was a depolarization and a decrease in membrane conductance. This is also consistent with block of inward rectifying channels. If the inward rectifier channels such as those seen in the soma are also present in the afferent terminals their block may be responsible for the activating effect of CAPS on sensory terminals. DHHS-NS11453.

19.4

EFFECTS OF VARIOUS NEUROTOXINS ON PHENYLETHANOLAMINE N-METHYL-TRANSFERASE (PNMT) ACTIVITY OF RAT RETINA. Joseph Cohen. Department of Pharmacology, Graduate School of Arts and Sciences, Howard University, Washington, D.C. 20059.

In utilization of neurotoxic agents in retinal research, it will be of advantage to find agents that can selectively destroy specific cell types while sparing others, in order to elucidate the physiological functions of specific pathways and cell types in the CNS. Various neurotoxins were administered intravitreally to ether anesthetized rats in order to determine if the PNMT-containing amacrine cells are susceptible to the toxic effects of these agents. PNMT activity was measured by radiometric assay. Toxicity was determined by comparing PNMT activities of retinas from drug-treated to those from saline-treated eyes. Agents used were kainic acid 10nm, ibotenic acid, 40nm and quisqualic acid, 125nm. Animals were sacrificed one week after injections. PNMT activity of kainate-treated eyes was 17%, quisqualate-treated eyes 38%, and ibotenate-treated eyes 92% of controls. These results demonstrated that the PNMT-containing cells are resistant to the toxicity of some neurotoxic agents, in this case ibotenic acid. Other investigators have demonstrated that acetylcholine-containing amacrine cells are very vulnerable to the toxic effects of ibotenate. Thus, ibotenate is not equally toxic to all cells in retina. These results support the suggestion by others that some cells types in the retina may be resistant to the toxic effects of ibotenate. (Supported by Howard University Research Development Grant, #529053).

19.5

A FLOURESCENCE TECHNIQUE FOR MEASUREMENT OF OXYGEN CONSUMPTION ($\dot{Q}_O$) OF SINGLE ISOLATED GIANT AXONS. Hargittai, P. T.*, Ginty, D. D.*, Lieberman, E. M., East Carolina Univ. School of Med., Dept. of Physiol., Greenville, N. C. 27834

Pyrene fluorescence is quenched by oxygen in an inverse and linear manner related to the partial pressure of $O_2$ in solution. We have developed a micro-chamber for measuring $\dot{Q}_O$ of a single axon, monitoring the change in fluorescence of a pyrene probe. The probe consists of a Spectra/Por dialysis hollow fiber filled with 2.5mM pyrene in paraffin oil. The probe is placed into a 1 mm i.d., 2 cm long quartz capillary tube with a 15 mm freshly dissected crayfish medial giant axon. The capillary is placed in an apparatus that forms an air and water tight seal except for a 0.2 mm i.d. stainless steel tube at both ends allowing for exchange of solutions. The apparatus is mounted on an Olympus inverted microscope equipped with epifluorescence optics and an HB0100 W/2 mercury lamp. Fluorescence intensity is monitored with an EMI 124/B photomultiplier tube attached to the T.V. port of the microscope. An IMT2-DMU filter unit is utilized to select an excitation wavelength of 350 nm and collect emitted light of above 420 nm. The signal is amplified with a Keithly 480 picoammeter and recorded on a strip chart. Measured $\dot{Q}_O$ data agree with high energy phosphate utilization previously measured in this laboratory. Infusion of crayfish saline with 3X normal $K^+$ results in a 2.5 times increase in $O_2$ consumption. Supported in part by ARO DAAL03-86-0023.

19.6

TOPOGRAPHICAL ORGANIZATION OF SOMATOSENSORY CORTICES (SI AND SII) OF THE NEONATAL PIG. Sandra L. Craner* and Richard H. Ray. East Carolina Univ., Greenville, N.C. 27834.

The primary (SI) and secondary (SII) somatosensory cortices of anesthetized neonatal pigs (2 hrs-3 wks old) were mapped using tungsten microelectrodes. Single and multineuronal spike activity was evoked by manual palpation. Previous studies (Adrian, 1943; Woolsey and Fairman, 1946) using evoked potentials determined the loci of the SI representation for the snout and forelimb areas and of the SII representation for the face, forelimb, and hindlimb areas. However, the SI hindlimb and trunk and the SII trunk subdivisions were not described. This study provides detailed complete body representations in both SI and SII of neonatal pigs. Other than the enlarged snout and proximal forelimb representations on the lateral surface of the hemisphere, most of the SI body representation (hindlimb, trunk and ventral forehoof) is located on the mesial wall. At this developmental stage, much individual variation exists in the trunk and hindlimb representation in SI. Unlike other ungulates, some piglets exhibit comparatively large representations of the trunk and hindlimb directly bordered by the forelimb area and the neurons respond to light cutaneous and hair stimulation. In SII, the face, forelimb, hindlimb and trunk subdivisions of SII are clearly delineated in an inverted orientation. In general, the body representation of SI and SII in neonatal pigs appears similar to that found in older animals. (Supported by a grant from Sigma Xi).

19.7

TREATMENT OF NERVE CRUSH INJURY WITH HELIUM-NEON LASER IRRADIATION ENHANCES RECOVERY OF FUNCTION. T. Kevin Robinson* and Richard H. Ray. School of Medicine, East Carolina University, Greenville, NC 27834-4353

Based largely upon clinical observations, a variety of beneficial effects have been attributed to "biostimulation" with low energy laser radiation. This study was performed to assess the effects of the Helium-Neon laser upon the regeneration of the peroneal nerve following nerve crush. The peroneal nerves of 12 anesthetized rabbits were exposed bilaterally. Nerve damage was produced with a padded hemostat, the tissues were repositioned and the skin closed. The injury was made at a site remote from the skin incision so that normal skin would lie in the path of the laser radiation. The nerve to receive treatment was randomly chosen for each animal. The treated group received a total of 3 min. of laser irradiation daily (632.8 nm, .5 milliwatts) presented as 30 sec. exposures to each of 6 skin sites. Amplitudes and integrated voltages of activity evoked by electrical stimulation proximal to the sites of injury and recorded distally were used to assess recovery. Measurement of evoked activity was made at 3 day intervals for 15 days. It was found that the treated nerves showed an average recovery of 66% of pre-lesion levels of activity whereas the control group showed a 53% recovery. Recovery of function as determined by both amplitudes and integrated voltages for the evoked activity was significantly greater ($p < .01$) for the treated group. (Supported by Sigma Xi, APTA and NCPTA).

19.8

A BRIEF HISTORY OF THE EARLY USE OF ELECTRICITY IN MEDICINE. Stacy, R. W., Stacy, S. M., Hendershot, D. M. and Petrofsky, J. S., National Center for Rehabilitation Engineering, Wright State University, Dayton, Ohio 45435. The use of electricity in medicine has roots which extend to the time around the birth of Christ when electric eels and black torpedo fish were used to relieve headache pain. In the 17th century, invention of the electrostatic sulfur sphere provided the first controlled artificial production of electricity. Hauksbee elaborated the sphere into an electrostatic generator in the early part of the 18th century. In combination with Leyden jars, this generator increased the medical applications of electricity to control pain. In the 19th century, electricity was combined with acupuncture from Asia to provide more localized pain relief. In the 1790's, Galvani found that frogs' legs twitched when given a shock from an electrostatic machine. Galvanism using a voltaic pile began being used extensively but fell into disrepute because of exploitation by quacks and charlatans. Faraday's invention of the transformer in 1831 led to studies on the effects of electricity on various diseases, to its application to paralyzed muscle to restore movement, and to devices for electrocautery, electrocardiography, X-rays, and electrical illumination of accessible body cavities.

This paper is dedicated to the memory of Dr. Ralph W. Stacy, who passed away March 6, 1986, during its preparation.



23.1

ELECTROGENIC ATP-DEPENDENT $Cl^-$ ACCUMULATIVE TRANSPORT IN PLASMA MEMBRANE VESICLES FROM APLYSIA GUT. G.A. Gerencser. Dept. of Physiology College of Medicine, Univ. of Florida, Gainesville, FL. 32610 (U.S.A.).

The serosa negative transepithelial potential difference across Aplysia gut is generated by a $Na^+$ and $HCO_3^-$ -independent active electrogenic $Cl^-$ absorptive mechanism. Additionally, a $Cl^-$-stimulated ATPase activity and an ATP-dependent $Cl^-$ transport process was found in Aplysia enterocyte plasma membranes. In an attempt to further elucidate this transport process plasma membrane vesicles from Aplysia enterocytes were prepared utilizing differential centrifugation and sucrose density gradient techniques. Electrogenicity of the ATP-dependent $Cl^-$ transport was confirmed in three ways. First, an inwardly directed valinomycin-induced $K^+$ diffusion potential, making the vesicle interior electrically positive, enhanced ATP-driven $Cl^-$ uptake compared with vesicles lacking the ionophore. Second, an inwardly directed FCCP-induced $H^+$ diffusion potential, making the vesicle interior less negative, increased ATP-dependent $Cl^-$ uptake compared to control. Third, ATP plus $Cl^-$ increased intravesicular negativity measured by lipophilic $TPMP^+$ distribution across the vesicular membrane. Both vanadate and thiocyanate inhibited the ATP plus $Cl^-$-dependent intravesicular negativity. These results are consistent with the hypothesis that the active electrogenic $Cl^-$ transport mechanism in Aplysia intestine could be a $Cl^-$-stimulated ATPase found in the enterocyte plasma membrane. Supported by DSR No. 122101010.

23.2

**HYPER-OSMOTIC WATER TRANSPORT IN THE RECTUM OF AN INSECT: EPITHELIAL WATER-ION COUPLING.** *John Machin.* University of Toronto, Toronto, Ontario, Canada, M5S 1A1.

The mealworm rectal complex, one of the most powerful water reabsorbing structures known, is capable of extracting liquid water or vapor down to activities of 0.88. Standing osmotic gradients established in six Malpighian tubules act as a concentrated "osmotic sink" (6.7 $Osmols.kg^{-1}$) surrounding the rectum. Since the structural arrangement of the tubules is incompatible with their functioning as counter-current multipliers, such high osmotic pressures must depend on impressive "uphill" ion transport, combined with controlled water entry. A key role is apparently played by the perinephric membrane, a peripheral structure, acting as a selective barrier, separating the tubules from the blood (0.3 $Osmols.kg^{-1}$). Microelectrode studies suggest that ion (KCl) concentration is a two stage process with the perinephric membrane actively transporting $K^+$ in specialized regions from the blood to the tubule cells. However over most of its surface the perinephric membrane is composed of multiple layers of collapsed cells, suggesting how it also acts as a barrier to water.

(Supported by Natural Sciences and Engineering Research Council, Canada. Operating Grant A1717).

23.3

UNEXPECTED NORMAL AND ANOMALOUS PD RESPONSES TO CHANGES IN STROMA K (Ks) IN FROG CORNEA EPITHELIUM. G. Carrasquer, R. Luo*, W. S. Rehm, M. Schwartz and M. Dinno. Univ. of Louisville, KY 40292 and Univ. of Mississippi, Oxford, Miss. 38677.

Normal PD responses to changes in Ks are usually obtained. Anomalous PD responses to changes in Ks are obtained only after exposure to 0 mM Ks (AJP:F185,1985). Anomalous PD responses have been attributed to the electr. Na-K ATPase pump when the resist. of the simple K cond. (RK) is high (both pathways in the basolateral (BL) memb.). Using the same in-vitro technique: (1) RK was incr. by decr. intracell. K (Kc), inducing K diffusion through the apical (A) memb. with $10^{-5}$ M. amphotericin B (AmB) in 4 mM K tear soln. A decr. of Ks from 4 to 0 mM gave a decr. (unexpected-anomalous) PD of 3.2 from 21.2 mV; an incr. in Ks from 0 to 4 mM gave an incr. (expected-anomalous) PD of 2.4 from 16.7 mV. (2)RK was decr. by incr. tear K from 4 to 79 mM in the presence of AmB to maintain a high Kc. A decr in Ks from 4 to 0 mM gave an incr. (exp.-normal) of 8.4 from 32.8 mV; an incr. in Ks from 0 to 4 mM gave a decr. (unexp.-normal) of 6.2 from 36.3 mV. (3) Parenthetically, an incr. in tear K from 4 to 79 mM, in the presence of AmB, gave an incr. of 10.3 from 21.2 mV consistent with the opening of a K cond. pathway in the apical memb. Anomalous PD responses to changes in Ks result only when RK is high, leaving the electrogenic Na-K ATPase pump as dominant K pathway in the BL membrane. (NIH support).

23.4

USE OF ELECTROCHROMIC DYES TO IDENTIFY MITOCHONDRIA-RICH CELLS IN FROG SKIN. James T. Blankemeyer, Wolfram Nagel, and Douglas Kliewer.* Dept. of Zoology, Oklahoma State University, Stillwater, OK 74078

Mitochondria-rich cells (MR) have been implicated in chloride transport. Electron microprobe evidence has demonstrated that MR cells are not part of the syncytium of epithelial cells in the frog skin. The flask-like appearance of the MR cells makes visual identification straightforward. Electrochromic dye, usually 3,3' dipentyloxacarbocyanine (Di-0-C5(3), varies fluorescent intensity with PD. Although electrochromic dyes have been used extensively on single-cell preparations, they have not been successfully used on epithelia We used the dyes to test whether the MR cells have a PD (and thus a fluorescence) distinguishable from the syncytial cells. Application of electrochromic dye to chamber-mounted, split frog skin reveals three sources of fluorescence. The first is from the nuclei of the stratum corneum. The second source was apparent MR cells which are located 12 microns below the surface and are circular when viewed from above. Double staining with Rhodamine 123, which binds mitochondria, shows that about 85 percent of the cells visible with electrochromic dye were also stained with Rhodamine 123. The third source of fluorescence was from the skin glands. The above results suggest that electrochromic dyes may be valuable for marking cells and measuring cellular PD in frog skin and in other epithelia.

23.5

RUBIDIUM TRANSPORT ACROSS THE RABBIT COLON: BILE SALT-INDUCED SECRETION. R.W. Freel (Spon: T.H. Dietz). Dept. Zoology-Physiology, Louisiana State University, Baton Rouge, LA 70803

Dihydroxy bile salts, such as taurochenodeoxycholate (TCDC), markedly alter the permeability and transport properties of the mammalian large intestine. This study examined the effects of TCDC on $Rb^+$ (a $K^+$ analog) transport across the isolated, short-circuited distal colon of the rabbit. In controls, the unidirectional fluxes of $^{86}Rb$ were: $J_{sm}^{Rb}$ = .25±.02 and $J_{ms}^{Rb}$ = .59±.07 $\mu$Eq · $hr^{-1}$ · $cm^{-2}$. These values are similar to the reported values for $^{42}K^+$ fluxes across this tissue under similar conditions. Mucosal $Ba^{+2}$ (4mM) and serosal ouabain ($10^{-4}$M) increased net $Rb^+$ absorption by decreasing $J_{sm}^{Rb}$ to .09±.02 $\mu$Eq · $hr^{-1}$ · $cm^{-2}$. Serosal cAMP ($5x10^{-4}$M) or mucosal TCDC (2mM) stimulated net $Rb^+$ secretion chiefly by increasing $J_{sm}^{Rb}$ to approximately .67±.09 $\mu$Eq · $hr^{-1}$ · $cm^{-2}$; in both cases mucosal barium or serosal ouabain reversed the effects of these secretagogues. Pretreatment of tissues with the calcium-calmodulin antagonist trifluoperazine ($10^{-4}$M, serosal) prevented both cAMP- and TCDC-induced $Rb^+$ secretion. These results demonstrate that luminal bile salts promote $Rb^+$ (and by analogy, $K^+$) secretion by pathways that are similar to those produced by cAMP (i.e., not a simple detergent-induced lysis) and may involve the action of a calcium-calmodulin complex.

23.6

IONIC-DEPENDENCE OF ACID FORMATION BY PERMEABLE GASTRIC GLANDS. S.J. Hersey and L. Steiner*. Emory University, Atlanta, GA 30322.

Isolated gastric glands made permeable with digitonin were employed to investigate the ionic dependence of ATP-stimulated acid formation. In order to enhance the sensitivity of the measurement, radiolabeled benzylamine was substituted for aminopyrine as a probe for measuring acid formation. In buffered sucrose medium, ATP addition results in little or no acid formation. Acid formation could be induced by subsequent addition of KCl, to lesser degree by $K_2SO_4$, but not by NaCl, $Na_2SO_4$ or choline chloride. Anion selectivity of acid formation, in the presence of K, showed a sequence of Cl=I>Br> $NO_3$>>$SO_4$=isethionate. Fluoride was found to inhibit acid formation. Valinomycin enhanced acid formation in the presence of KCl but not with $K_2SO_4$ or Kisethionate. The valinomycin stimulation was significantly greater in glands made resting by pretreatment with cimetidine than in glands prestimulated with forskolin. These observations support the concept that a transition from resting to stimulated state involves the introduction of a K permeability in the secretory membrane of the parietal cell. (Supported by NIH AM14752 and AM36548).

23.7

ROLE OF K POTENTIALS IN ELUCIDATING NATURE OF FROG GASTRIC PROTON PUMP WITH Cl FREE MEDIA. W. S. Rehm, G. Carrasquer, M. Schwartz and M. Dinno. University of Louisville, KY 40292, and University of Mississippi, Oxford, Mississippi 38677.

In secreting mucosae, with Cl free ($SO_4$ for Cl) media, the nutrient side is negative and inhibition increases PD (e.g., from -25 to 5 mV. The orientation and $\Delta$PD is evidence for electrogenic model, i.e., inhibition abolished $E_H$, the emf of pump). Hersey et al (AJP 248:G246) offer explanation of above on basis of neutral pump model -- the inverted PD is due to K diffusion potential from cell to lumen (they ignore K diffusion potential from cell to nutrient) and the $\Delta$PD results from decrease in K potential -- with inhibition K continues to enter lumen and its conc. increases (e.g., from 2 to 6 mM) resulting in decrease in K potential thus explaining increase in PD. We tested neutral model by first increasing K from 4 to 80 mM in secretory fluid (which increases PD from about -25 to 15 mV) and then producing inhibition. With 80 mM K continuing entrance of K into lumen would produce little change in K(cell)/K(lumen) -- hence neutral model predicts negligible $\Delta$PD. Contrary to this prediction with 80 mM K, the PD due to inhibition (SCN or omeprazole) is about 23 mV (e.g., PD from 15 to 38 mV) -- predicted by electrogenic model (i.e., $E_H$ goes to zero). We implicitly assume low resistance (R) path is via lumen and oxyntic cells and parallel paths have high R. By use of hypotonic technique it will be shown that this assumption is justified. (NSF support).

23.8

SITE OF ION SELECTIVITY OF THE CRAYFISH BLOOD-BRAIN BARRIER. Butt, A. M.*, Hargittai, P.* & Lieberman, E. M., East Carolina Univ., Sch. Med., Greenville, N.C. 27834.

The perineurial sheath surrounding the ventral nerve cord of the crayfish is highly selective to $K^+$, being almost impermeable to other monovalent cations. However, the site of selectivity was unclear: the mucopolysaccharide layer at the sheath surface, membranes of the glial cells which make up the sheath, or ion selective tight junctions between the glial cells. Superfusion with 100mM $K^+$ causes a rapid change in the potential difference across the sheath to +42mV, used to evaluate ion selectivity, followed by a fall in potential to a plateau around +25mV, a measure of sheath permeability. The axon membrane potential depolarizes slowly 5-10mV over a 2 minute 100mM $K^+$ pulse and is a measure of the $[K^+]$ in the adaxonal space. Superfusion with 1% NaCN + 1% iodoacatic acid (30 mins) had no effect on sheath selectivity or permeability. Opening of the intercellular junctions by osmotic shock (NCS+100mM mannitol) had no effect on the selectivity of the sheath, but increased the permeability to $K^+$ 3-4 times. Bathing the cord in 1% hyaluronidase or ruthenium red for 30 mins almost completely abolished the selectivity of the sheath but did not increase its overall permeability. The results suggest the site of ion selectivity is the mucopolysaccharide layer, acting as a highly efficient ion exchanger, which is quite separate from the reduced permeability of the sheath due to the intercellular junctions. Supported in part by ARO DAAL03-86-0023.

24.1

BRADYKININ IS NOT INVOLVED IN EARLY CANINE ENDOTOXIC SHOCK. H.F. Janssen, J.L. Pugh,* D.L. Lange,* C.D. Williams,* and S.D. Leffew*. Depts. of Ortho. Surg. and Physiol., Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Previous work in this and other laboratories have demonstrated that captopril exacerbates the hypotension produced in dogs by endotoxin. This depresser effect of captopril could be due to the potentiation of bradykinin(BK) or inhibition of angiotensin II (AII) formation. The current study employed anesthetized adult mongrel dogs. The right femoral vein and artery were cannulated for the administration of drugs and monitoring of arterial pressure. A tracheostomy was performed and the animals were respired with room air. It was found that after endotoxin injection (0.5 mg/kg) a AII receptor blockade ($Sar^1$,$Ile^8$-AII) produced a mean arterial pressure (MAP) response statistically similar to that seen when captopril (0.2 mg/kg Bolus + 5 ug/kg/min) is given in combination with endotoxin. While these results suggest an absence of BK production, the possibility of BK receptor inactivation during endotoxin shock cannot be disregarded. Additional studies suggested that BK injections (5 ug/kg) can further depress MAP in the dog after endotoxin injection and that this depresser effect of BK is potentiated by captopril. Based on these results, it can be concluded that in the early phases of canine endotoxin shock AII plays a significant role in the maintenance of MAP and that BK is not produced in sufficient quantities to lower MAP. This work was supported in part by NIH Grant #GM35186-01A1.

24.2

PROSTAGLANDINS DO NOT MEDIATE ENDOTOXIN-INDUCED ALTERATIONS IN GLUCOSE METABOLISM. CH Lang, GJ Bagby, HL Blakesley* and JJ Spitzer. Physiology, LSU Med. Ctr., New Orleans, LA 70112.

The plasma concentrations of prostaglandins (PGs) are elevated during sepsis, and infusion of PGs into control animals produces changes in glucose metabolism consistent with those seen in sepsis. Thus, the present study determined if cyclooxygenase products of arachidonic acid were responsible for the altered glucose kinetics seen during hypermetabolic sepsis. Sepsis was induced in chronically catheterized conscious rats by multiple injections of live E. coli ($10^{10}$ organisms) via a subcutaneous catheter; control animals received sterile saline. Control and septic rats received multiple i.v. injections (every 8 hrs) of indomethacin (INDO; 5mg/kg) or vehicle. Glucose kinetics were assessed in 24 hr fasted rats using a constant i.v. infusion of [6-3H]-glucose. Sepsis increased colonic temperature (+2°C), plasma lactate (55%), rate of appearance for glucose (Ra, 33%) and glucose recycling (63%) in vehicle-treated rats. INDO reduced temperature in septic rats to control values; however, the elevation in lactate (98%), glucose Ra (65%) and recycling (78%) were still evident. These results indicate that doses of INDO capable of reducing the sepsis-induced febrile response fail to affect the alterations in carbohydrate kinetics, suggesting that products of the cyclooxygenase pathway are not important mediators in the development of the glucose dyshomeostasis seen in hypermetabolic sepsis. (Supported by NIH GM 32654).

24.3

MEASUREMENT OF PLASMA THROMBOXANE AND PROSTACYCLIN CONCENTRATIONS DURING COBRA VENOM FACTOR-INDUCED COMPLEMENT ACTIVATION IN RABBITS. John T. Flynn. Thomas Jefferson University, Philadelphia, PA 19107.

Recent studies have shown that components of the complement system are able to stimulate eicosanoid production both in vivo and in vitro. Since endotoxin activates the complement cascade, it has been hypothesized that endotoxin-induced eicosanoid production in intact animals may be due to complement activation. To test this, anesthetized rabbits were subjected to complement activation with cobra venom factor (CVF). Complement titers were measured with a RBC lytic technique while eicosanoids were quantified by specific RIA. Control group rabbits (n=7) received saline vehicle and were observed for a 60 min period. These animals had stable arterial pressure, white blood cell count, CH50 complement titer, and venous plasma prostacyclin and thromboxane concentrations. In contrast, rabbits which received a bolus injection of 40 U/kg CVF at time zero (n=9) demonstrated a slightly depressed arterial pressure, a significantly lower WBC count, and a complement titer which fell significantly within 5 min and was only 19+/-3 % of the control group value at 60 min. Neither plasma prostacyclin nor thromboxane concentrations changed significantly in the CVF-treated animals. These data suggest that activation of the endogenous complement system in an intact animal can proceed without significant activation of the arachidonic acid cascade. Supported by NIH GM 28023.

24.4

Mechanism of skeletal muscle insulin resistance during endotoxin shock in the dog. R.M. Raymond, Loyola Univ.,Maywood IL. 60153 and the VA Hosp. Hines, IL 60141.

Recent data has suggested that muscle insulin resistance due to obesity and diet could be prevented with adenosine antagonist. The present study was undertaken to test the hypothesis the skeletal muscle insulin resistance during acute endotoxin shock is mediated via adenosine. Large mongrel dogs were anesthetized, intubated and ventilated artificially. The constantly perfused gracilis muscle preparation was used. Shock was induced by the i.v., infusion of 1mg/kg Salmonella Typhymurium endotoxin. Insulin was infused locally, intra-arterially at a concentration, of 300-500 mU/min. Adenosine (ADO) ($10^{-2}$mol) was infused with insulin during a control period and adenosine deaminase (ADA) was infused with insulin following one hour of shock. During control, insulin increased glucose uptake from .32 to 1.16 mg/min. However, adenosine together with insulin returned glucose uptake to control values. During shock, insulin did not stimulate muscle glucose uptake. Adenosine deaminase together with insulin resulted in elevated glucose uptake (.45 to .88 mg/min. These data indicate that adenosine induces an "insulin resistant" state during control. One hour following shock, gracilis muscle was refractory to insulin and was reversed with adenosine deaminase. These data support the hypothesis that adenosine mediates insulin resistance during acute endotoxin shock. (Supported by HL-31163 and the VA)

24.5

MEDIATORS OF HIGH CARDIAC OUTPUT ENDOTOXEMIA. D. Traber, D. Herndon, G. Schlag*, H. Redl*, J. Flynn, L. Woodson*, L. Traber*. Univ. Tx. Med. Br. & Shriners Brns. Inst., Gal., TX 77590 & Boltzman Inst. of Traum., Vienna, Austria & Thom. Jeff. Coll. of Med., Phil, PA 19107

Continuous administration of endotoxin (LPS)(24 ng/kg/hr) will result in a high cardiac output (CI), a low systemic vascular resistance (TPR) and an increase in lung lymph flow (LQ). We evaluated the mediators released during this hyperdynamic response. Eight sheep were prepared by implanation of cardiopulmonary catheters. At 7 days post surgery, control data were obtained and LPS was administered (24 ng/kg/hr). Four hours after administration of LPS, CI began to rise and remained elevated for 10 hours. This rise in CI was associated with a fall of TPR and an increase in LQ. With the rise in CI, there was a reduction in plasma prekallikrein (KK) and C1 esterase inhibitor activity (C1I). Blood levels of prostaglandin 6 keto F1 alpha (PG), thromboxane B2 (TXa), and beta endorphin (EN) did not change statistically. Conclusion: Increases in CI and LQ associated with LPS occur with evidence of the activation of the kallikrein/bradykinin system, with little evidence of changes in endogenous opiates or eicosanoids.

| | CI | TPR | PAP | LQ | KK | C1I | EN | TXa | PG |
|---|---|---|---|---|---|---|---|---|---|
| Control | 6.5 | 1156 | 20 | 6.2 | 100 | 11.3 | 5.1 | 466 | 500 |
| Post lps | 8.1* | 898* | 24 | 16.8* | 83* | 10.4* | 6.1 | 487 | 497 |

* = p less than 0.05 by ANOVA

24.6

MODULATION OF SEPTIC SHOCK BY IMMUNE STIMULATION. D. Williams*, E. Sherwood*, W. Browder*, R. McNamee*, E. Jones* and N. Di Luzio. Depts. of Physiology and Surgery, Tulane Medical School, New Orleans, LA 70112.

Previous studies (Williams et al., Surgery 93:448,1983) have shown that administration of the biologic response modifier glucan will enhance survival, decrease bacteremia and maintain macrophage functional status in a murine model of gram-negative intra-abdominal sepsis. The present study was undertaken to examine time and dose response relationships of glucan prophylaxis in the modification of Escherichia coli induced sepsis. Additional studies were undertaken to examine immunologic parameters following glucan administration. Male ICR/HSD mice (18g) were injected IP with glucan (1 mg/mouse) at varying time intervals prior to and following IP challenge with 1 x $10^8$ E. coli. Time-response data revealed that glucan significantly ($p<0.05$) enhanced survival in mice with E. coli sepsis up to 6 hrs. prior to septic challenge. Dose-response studies established that IP glucan would exert a significant ($p<0.05$) effect on survival at doses as low as 1 mg/kg. In vitro splenocyte proliferation and splenocyte response to mitogens were increased ($p<0.01$) by IP glucan. In vitro bone marrow proliferation showed a 104% increase ($p<0.01$) following IP glucan. We conclude that: 1) glucan enhances survival in mice with fulminant sepsis over a wide dose and time response range; 2) glucan stimulates diverse immune parameters; and 3) non-specific immune stimulation with biologic response modifiers may be of value in the modification of septic shock.

24.7

REVERSAL OF SEPTIC-INDUCED LACTATE ACIDEMIA BY DICHLOROACETATE: ROLE OF DECREASED PYRUVATE DEHYDROGENASE ACTIVITY. Thomas C. Vary, John H. Siegel, J. Glenn Morris*, Ben Tall*. MIEMSS, University of Maryland, Baltimore, MD 21201

Sepsis is characterized by elevated plasma lactate concentrations. The hyperlactatemia could be explained by decreases in the % active pyruvate dehydrogenase complex (PDHa). Dichloroacetate (DCA) reduces circulating lactate concentrations by stimulating PDH activity allowing increased carbohydrate flux through the complex. The effect of DCA (1 mmol/kg body wt) on serum glucose, lactate and tissue lactate and PDHa was investigated in rats with a large intraabdominal abscess. Liver and skeletal muscle were frozen in situ seven days following the intraperitoneal introduction of a rat fecal-agar pellet (1.5 ml) inoculated with a known bacterial flora (sterile vs E. coli $10^4$/ml + B. fragilis $10^8$/ml) which generated an abscess. DCA significantly increased the %PDHa in both liver and skeletal muscle. In liver, DCA increased the %PDHa to the same extent (>85%; p<0.001) in all conditions. Unlike liver, in skeletal muscle from septic animals, increases in %PDHa after DCA were significantly less (50±4%) than in either C or I (>85%; p<0.05). However, the stimulation of PDHa was sufficient to lower both tissue and plasma levels of lactate. The lower lactate levels with DCA were not a consequence of hypoglycemia. Hence, DCA may provide a pharmacological method for promoting glucose oxidation and reducing lactate acidemia associated with chronic severe sepsis by activating PDH. NIH 1-RO1-GM36139-01

24.8

MEFENAMATE INHIBITS PRE AND POST GLOMERULAR ARTERIOLE DILATION IN RESPONSE TO LIVE E.COLI SEPSIS. H.M. Cryer*, R.N. Garrison*, P.D. Harris, and J.T. Fleming. Depts of Surgery and Physiology, University of Louisville, Ky. 40292.

To determine if prostaglandin mediated vasodilation of the renal microcirculation occurs during sepsis, chronic unilateral hydronephrosis was induced in male Sprague-Dawley rats (n=6) by ligation of the left ureter. Two months later, rats (400-500 gm) were anesthetized with urethane (800 mg/kg), and the hydronephrotic kidney was bisected and suspended with intact neurovascular connections over an optical port in an environment-controlled Krebs tissue bath. Diameter measurements were made of interlobular, afferent, and efferent arterioles during a baseline period, after intravenous infusion of $1x10^7$ $CFU_4$ live E.coli, after addition of mefenamate to the bath ($10^{-4}$M), and after wash-out of the mefenamate. Results, expressed as percent (%) change from baseline values (+% = dilation, -% = constriction), were:

| * = p<0.05 | IL | AFF | EFF |
|---|---|---|---|
| BASELINE | 20.7 ± 2µ | 10.5 ± 1µ | 11 ± 1µ |
| E.coli | +13 ± 2% * | +51 ± 11%* | +37 ± 8% * |
| MEFENAMATE | -10 ± 5% | + 1 ± 4% | +15 ± 5% * |
| WASH | +10 ± 4% | +46 ± 7% * | +37 ± 11%* |

In addition, no dilation occurred when the bath contained mefenamate prior to administration of E.coli. We conclude that live E.coli bacteremia results in dilation of pre and post glomerular arterioles, and that this dilation is mediated by increased prostaglandin synthesis.

24.9

EFFECT OF HEMORRHAGIC SHOCK ON BRAIN. George G. McDonald* and Jureta Horton, Departments of Radiology and Surgery, The University of Texas Health Science Center at Dallas, Dallas, Texas 75235

P-31 nuclear magnetic resonance (NMR) was used to determine the effect of hemorrhagic shock on dog brain. A 5cm patch of scalp was removed from anesthetized dog and a 4cm surface coil held against the skull by sutures to adjacent tissue. After baseline NMR spectra were obtained, the animals were bled to a mean arterial pressure of 30-35 Torr for two hours. The intracellular pH ($pH_{IC}$), as measured from inorganic phosphate chemical shift, decreased monotonically from a pre-shock value of 7.21±.07 (mean ± S.E.), N=7; to 7.12±.15 at 30 minutes and 7.04±.09 at 90 minutes of shock, parallelling a more rapid decline in arterial blood pH from 7.27±.03 to 7.01±.02 (P=.001). No significant changes in phosphocreatine (PCr) or in ATP concentrations were detected during two hours of shock. Cerebral flow dropped from 0.521±.06 ml/min/gm wet weight before shock to .464±.05 at 15 minutes of shock and .339±.05 (P=.05) at 120 minutes of shock. A separate group of control dogs, N=6, were anesthetized for two hours. No changes in [PCr], [ATP], or $pH_{IC}$ were observed over two hours in this group. Our data indicate that shock induced cerebral ischemia does not deplete ATP stores, probably due to decreased ATP utilization during a low flow state.

24.10

METABOLIC ALTERATIONS DURING CHRONIC PERITONITIS IN THE DOG. Howard Heppe, M.D.,* and Richard Raymond, Ph.D., Loyola Univ. Maywood, IL 60153 and the VA Hosp., Hines, IL 60141

Stress, whether in the form of severe trauma, burn, or infection has been shown to cause catabolism of endogenous protein in humans. Lack of an adequate animal model has made it difficult to study this metabolic problem. The goal of the present study was to design a model of chronic sepsis which would accurately reflect this metabolic change. Adult mongrel dogs were studies over a ten day protocol. Following control metabolic determinations, peritionitis was induced by implanting a Fecal soaked sponge amid the intestines. Aminals were then monitored daily for one week. Results showed all dogs to be in a baseline positive nitrogen balance which shifted to a negative nitrogen balance after the induction of sepsis, (+7.0 to -5.9 $gN_2$/Day). This was accompanied by a 10-20% loss in body weight. Additionally, ketone levels fell from a baseline of .9uM/ml. to .44uM/ml. In summary, the dogs entered a state of negative nitrogen balance and anorexia. Despite their anorexia, the dogs were not ketotic indicating a lack of either fat utilization and/or ketogenesis. This is an accurate reflection of the changes seen in humans during chronic sepsis, in which the stress produces significant proteolysis without a concommitant increase in lipolysis. Further study will be necessary to determine the etiological factor of the protein loss, and to determine therapeutic interventions to manage this problem. (Supported by HL-31163 and The VA)

## CHEST WALL MECHANICS

25.1

RELATIVE EXCURSIONS OF THE RIBCAGE AND ABDOMEN IN RABBITS DURING SINUSOIDAL FORCING FROM 0.5 TO 30 HZ. B.R. Boynton*, I.D. Frantz, III, B.G. Buckley*, and J.J. Fredberg. Department of Pediatrics, New England Medical Center, Tufts University and The Biomechanics Institute, Boston, MA 02111

We measured the amplitude of ribcage and abdominal excursions in 12 anesthetized rabbits during sinusoidal volume changes (0.5 to 30 Hz) delivered through a tracheostomy. All measurements were made with the animals on their left side. Tidal volume was measured by body plethysmography and regional chest wall excursions were measured by inductive plethysmography. During oscillations at fixed tidal volume (Vt = 1.3 ml/kg) the normalized ratio of ribcage (RC) to abdominal (ABD) excursions decreased from 1.1±0.1 at 2 Hz to 0.9±0.1 at 6 Hz. As frequency increased further RC/ABD rose sharply, reaching a plateau of about 6.6 between 20 and 30 Hz. In 6 additional rabbits we measured chest wall excursions while varying Vt between 0.5 and 3.7 ml/kg. RC/ABD was independent of Vt at low frequencies (0.5-4 Hz) but increased with Vt between 8 to 30 Hz, rising sharply at the higher frequencies. RC and ABD excursions were nearly synchronous from 0.5 to 2 Hz, but as frequency increased ABD lagged RC progressively, reaching a phase difference of 90° at 6-8 Hz and 180° between 16 and 20 Hz. These results are consistent with a chest wall model having a non-linear compliance associated with the ribcage in parallel with an inertance-resistance-compliance associated with the abdomen.
Supported by HL 34616 and HL 33009

25.2

EFFECT OF GRAVITY ON THE PARALYZED CANINE DIAPHRAGM. S. Krayer*, K. Rehder, J.R. Rodarte, and E.L. Ritman. Mayo Clinic and Mayo Foundation, Rochester, MN 55905.

To test the hypothesis that both shape and motion of the paralyzed diaphragm (di) are mostly gravity dependent, surface coordinates of the di at end-expiration and end-inspiration were determined using 3-D x-ray computed tomography (Dynamic Spatial Reconstructor). Three dogs (29-48 kg) were anesthetized (pentobarbital 30 mg/kg), paralyzed (pancuronium bromide 0.25 mg/kg), and their lungs were mechanically ventilated (tidal volume ($V_T$) = 16 ml/kg, f = 12 breaths/min); two dogs were studied while they were in both the supine and prone position, and one dog in the supine position only. Shapes of the di were compared in sagittal sections and motion was estimated from differences in the cephalocaudal coordinates of the di. We found that the shapes of the di relative to the field of gravity were similar but not the same in the prone and supine positions. Regardless of position, maximal motion occurred in dorsal and central regions, while ventral regions moved least. The di contribution to $V_T$ was similar in both positions (supine: 37-61%; prone: 51 and 63% of delivered $V_T$). The data suggest that gravity has a major effect on the canine di-shape while canine di-motion is apparently influenced to a large extent by other forces, such as thoraco-abdominal coupling.
Supported in part by NIH grant HL 04664.

25.3

PLEURAL LIQUID PRESSURE MEASURED WITH RIB CAPSULES IN PONIES. L. E. Olson and S.J. Lai-Fook, Ohio State U., Columbus OH 43210 and U. of California, San Francisco, CA 94110.

Pleural liquid pressure (PLP) was measured at FRC in 10 anesthetized ponies in the prone and supine positions. A capsule was implanted into a rib (#5, 6, 7 or 8) to measure PLP with minimal distortion of the pleural space (JAP 59:597, 1985). Capsule position relative to lung height was measured from thoracic radiographs. In the supine position, PLP was most negative in the nondependent lung regions and least negative in the dependent lung regions. The vertical gradient in PLP averaged -0.69 cm $H_2O$/cm height (n=10). PLP in dependent lung regions (<55% height) was near zero suggesting collapse of dependent lung regions. When measurements in regions above 55% lung height only were considered, the vertical gradient in PLP averaged -1.69 cm $H_2O$/cm height (n=7). These data are consistent with the poor ventilation distribution, reduced lung volumes and abnormal arterial blood gases observed in supine, anesthetized horses. In the prone position there was no significant vertical gradient in PLP which is consistent with the more uniform distribution of ventilation measured in this position. These results may be a consequence of the horse's stiff chest wall, diaphragm conformation, and lack of lobar fissures. (ALA of Ohio & OSU College of Vet Med Equine Research Fund).

25.4

VENTILATION DISTRIBUTION AFTER PNEUMONECTOMY IN RABBITS. G.P. Wilson III* and L.E. Olson. The Ohio State University. Columbus, Ohio 43210-1092.

To investigate the mechanical interaction between the heart and lungs, we measured lung volumes and ventilation distribution as a function of body position in 2 groups of rabbits: Group I consisted of 5 normal rabbits. Group II consisted of 5 rabbits which were studied 18 months after left pneumonectomy. In Group II rabbits in left lateral recumbency, the heart was beneath the remaining lung and in right lateral recumbency, the heart was above the remaining lung. FRC was measured by $N_2$ dilution, ERV was measured with a calibrated syringe and ventilation distribution was assessed from the single breath $N_2$ test by computing the ratio of the volume of phase IIIa to phase III. Results for Group I (2 lungs) and Group II (1 lung) follow:

| Lung Volumes | ERV (ml) | | | FRC (ml) | | |
|---|---|---|---|---|---|---|
| | Rt. Lat. | Lt. Lat. | Supine | Rt. Lat. | Lt. Lat. | Supine |
| Group I | 16.4 | 16.9 | 14.8 | 31.2 | 32.7 | 34.0 |
| Group II | 13.9 | 18.4 | 14.7* | 33.2 | 38.4 | 35.1* |
| Vent. Dist. - IIIa/III (%) | | | | | | |
| Group I | 82.4 | 83.6 | 78.5 | | | |
| Group II | 69.1 | 90.0 | 58.9* | | | |

(*- significant effect of body position by ANOVA)

We conclude that the heart compresses the remaining lung in right lateral recumbency and expands the remaining lung in left lateral recumbency in Group II rabbits. Similar effects may occur in each lung in normal rabbits because of the central position of the heart. (OSU Seed Grant.)

25.5

VENTILATORY RESPONSE TO SEVERE HYPOTENSION IN DOGS. S. Nava* and F. Bellemare* (SPON: J. Milic-Emili). Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada H3A 2B4

The ventilatory response to severe hypotension (H) induced by inflating a balloon in the right atrium (mean arterial pressure 50 - 70 Torr: Pa) was studied in 14 anesthetized dogs and compared to the response to $CO_2$ rebreathing (4 dogs) and 0.3 N HCl infusion (6 dogs). During H, 4 dogs died of cardiac arrest while 10 died of respiratory arrest after 67 ± 18 min of H. For the latter group we found: 1) An initial 1.8 fold increase in ventilation ($\dot{V}_E$) associated with the fall in Pa and not related to changes in $PaO_2$, $PaCO_2$ or pH. 2) This was followed by a 60% fall in $\dot{V}_E$ despite an increase in $PaCO_2$ to 56 Torr and fall in pH to 6.98 immediately preceeding apnea. This fall in $\dot{V}_E$ contrasted markedly with the 1.5 and 2.5 fold increase in $\dot{V}_E$ observed in normotensive dogs at pH 7.0 during HCl infusion and $CO_2$ rebreathing respectively. 3) The fall in $\dot{V}_E$ and transdiaphragmatic pressure (Pdi) with H were accompanied by a 30% fall in diaphragm EMG and 65% fall in parasternal intercostal EMG, indicating a progressive decrease in central neural drive. 4) The mean maximal Pdi measured in 6 dogs in response to 50 Hz bilateral phrenic nerve stimulation did not change significantly (less than 10%) with H, indicating that the diaphragm contractility was unimpaired. These results suggest that the terminal fall in $\dot{V}_E$ and ensuing apnea observed with severe hypotension are associated with a central neural depression of respiration possibly related to a severe reduction in brain blood flow. (Supported by the MRC of Canada, and Parker B. Francis Foundation).

25.6

COMPARISON OF RESPIRATORY AND PERIPHERAL MUSCLE FUNCTION DURING SUBMAXIMAL NEUROMUSCULAR BLOCKADE (SMNB). K. Brown*, S. Nava*, M. Sgro*, J. Milic-Emili and F. Bellemare*. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada H3A 2B4

The force-frequency curves for diaphragm and gastrocnemius muscles were studied in 6 pentobarbital anesthetized dogs during SMNB induced by constant infusion of succinylcholine 10 μg/kg/min. Using bilateral transjugular vein stimulation of phrenic nerves, transdiaphragmatic pressure (Pdi) and tracheal occlusion pressure (TOP) were recorded. Displacement of a strain gauge recorded gastrocnemius force. Each dog was studied during both mechanical (MV) and spontaneous ventilation (SV). For gastrocnemius during MV, SMNB depressed all frequencies equally, while for the diaphragm there was sparing of single twitch depression suggesting diaphragmatic resistance at lower stimulation frequencies. During SV, Pdi and TOP at 20 Hz and 50 Hz decayed at rates similar to those during MV. However, depression of diaphragmatic single twitch was accelerated. This depression was in contrast to gastrocnemius single twitch which was slower during SV. Ventilatory depression during SMNB followed the reduction in tidal volume. Reduction in tracheal occlusion pressure during SV paralleled the reduction in tidal volume. It also paralleled the reduction in 20 Hz and 50 Hz but not the single twitch depression. We suggest that the use of the gastrocnemius twitch to infer respiratory muscle function underestimates diaphragmatic function during MV and overestimates its function during SV. We also submit that the Pdi or TOP with single twitch stimulation is not an accurate assessment of ventilatory potential. (Supported by the Medical Research Council of Canada).

25.7

CRURAL-CRURAL DIAPHRAGM INTERACTION. A.F. DiMarco, G.B. Darian* and G.S. Supinski*. Case Western Reserve University, Cleveland, Ohio 44109.

Although the right and left crural diaphragm are anatomically oriented in parallel, their functional interaction is unknown. In 5 anesthetized dogs, we electrically stimulated the medial portions of the right and left crural diaphragm with bipolar stainless steel electrodes. Muscle shortening was assessed by measurements of in situ muscle length as determined by sonomicrometry. Force generation was assessed from trans-diaphragmatic pressure (Pdi). Unilateral stimulation resulted in muscle shortening of 30 + 2.5 SE% $L_R$ of the ipsilateral and 1.3 + 0.6 SE % $L_R$ of the contralateral crural diaphragm. The degree of shortening of each crura during synchronous bilateral stimulation was similar to that observed during respective unilateral stimulation of each muscle. Pdi produced by bilateral stimulation was similar to the arithmetic sum of that produced by separate right and left crural stimulation. We conclude that a) muscle shortening produced by unilateral crural activation does not substantially affect contralateral crural length, b) forces produced during unilateral crural stimulation summate during bilateral stimulation and c) despite their anatomic parallel arrangement, the right and left crural diaphragm do not interact according to a simple mechanical model of parallel arrangement. (Supported by NIH Grant #HL34143)

25.8

RESPIRATORY MOTOR RESPONSES TO DIAPHRAGMATIC FATIGUE. G.S. Supinski*, A.F. Di Marco, F. Hussein* and M. Altose Case Western Reserve University, Cleveland, Ohio 44109

The effect of respiratory muscle fatigue, independent of pulmonary and chemoreceptor inputs, on the level of respiratory motor drive is unknown. The present study examined the effect of diaphragmatic fatigue on respiratory motor output at constant levels of chemical drive. Innervated diaphragm strips were prepared in situ in 10 open chested, vagotomized, mechanically ventilated dogs. We recorded phrenic nerve activity (PN) to the strip, the contralateral diaphragm EMG (CD), the ipsilateral parasternal EMG (IP), and strip tension (T) generated during spontaneous breathing efforts. Fatigue was produced by occluding the phrenic artery supplying the strip for 20 minutes. $pCO_2$ was held at 55 mmHg in 8 occlusion trials and at 75 mmHg in 9 trials. Strip tension fell to 69+ 4 SE% ($p<0.01$) and 23 + 5 SE% ($p<0.001$) of baseline for $\bar{p}CO_2$ at 55 and 75 mmHg, respectively. There were significant increases in PN, CD, and IP. For example, PN rose to 177 + 22 SE% ($p<.01$) and 138 + 6 SE% ($p<.01$) of baseline for runs at $pCO_2$ of 55 and 75 mmHg, respectively. EMGs and ENGs returned to baseline within 20 minutes after release of occlusion. Results were similar for runs with simultaneous arterial and venous occlusion. We conclude that diaphragm muscle fatigue, produced by ischemia, results in a neurally mediated increase in respiratory motor drive. We speculate that this reflex is mediated by afferent fibers in the phrenic nerve.

25.9

REGIONAL VARIABILITY OF THE IN VIVO SHORTENING OF THE CANINE DIAPHRAGM DURING SPONTANEOUS BREATHING. J. Sprung*, C. Deschamps*, B.J. Walters*, J.R. Rodarte. Mayo Clinic and Fndn., Rochester, Minnesota 55905.

Diaphragm function in vivo has been studied using sonomicrometry, which has excellent temporal and spatial resolution but yields no information about diaphragm displacement. We adapted the biplane videofluoroscopic system previously used for regional lung deformation to study the diaphragm. Rows of 4-6, 2mm metallic spheres were stitched to the abdominal serosal surface along the course of individual muscle fibers of the left costal and crural diaphragm of beagle dogs. After a 3-week recovery period, the positions of these markers were determined at 30 Hz during spontaneous inspirations. Fractional changes in the separation between markers, 1.5-2.0 cm apart at FRC, were determined over multiple breaths. For this separation (similar to sonomicrometry) the change in distance between markers should closely approximate the shortening of the muscle fiber, even if the curvature changed. Preliminary results indicate substantial differences in fractional shortening between adjacent markers in a row, which are reproducible across breaths. The distance weighted average shortening along a row of 6-8 cm showed less variability between rows. These results suggest that a single fractional shortening measurement, which may vary with global, costal, or crural contractility, may be only an approximate measure of it. Supported by HL21584.

## CARDIAC MUSCLE PHYSIOLOGY

26.1

MYOCARDIAL CALCIUM COMPARTMENTATION: RESPONSE TO ALTERATION IN CALCIUM CHANNEL CURRENT. M.C. Fintel and G.A. Langer. U.C.L.A. Med. Center, Los Angeles, CA 90024

Calcium channel current was altered and the effect on myocardial calcium compartmentation investigated in cultured neonatal rat myocardial cells using the scintillation disk technique. Nifedipine reduced calcium uptake by 0.44±0.04 mmol/kg dry cell weight at 1.0 mM $Ca_o$ and 0.27±0.03 mmol/kg at 0.5 mM $Ca_o$. It reduced contractile amplitude by more than 70%. In contrast, the calcium channel agonist BAY k 8644 increased contractile amplitude by 55±7%. Despite the functional sensitivity of the cells to BAY k 8644, the agonist did not significantly affect calcium uptake at 1.0 mM $Ca_o$. Isoproterenol, which also augments calcium channel current, was likewise found not to affect calcium uptake at 1.0 mM $Ca_o$. Both BAY k 8644 and isoproterenol significantly increased calcium uptake at 0.5 mM $Ca_o$ by .17±0.04 mmol/kg and 0.20±0.01 mmol/kg, respectively. The increment in calcium uptake induced by isoproterenol and BAY k 8644 was completely and rapidly released (within one minute) by 10 mM caffeine. In conclusion, there exists in the myocardium a calcium compartment responsive to changes in calcium channel current. This compartment is saturated at 1.0 mM $Ca_o$, exchanges very rapidly, and is probably a caffeine-sensitive portion of the sarcoplasmic reticulum. This work was supported by NIH grants HL 28539-04 and HL 7412.

26.2

FORCE-LENGTH AREA CORRELATES BEST WITH OXYGEN CONSUMPTION IN ISOLATED PAPILLARY MUSCLE. R. Hisano* and G. Cooper Div. of Cardiology and Gazes Cardiac Res. Inst., VA Medical Center & Medical Univ. SC, Chaleston, SC 29403.

Pressure-Volume Area (PVA) of a ventricle has been shown to correlate well with myocardial oxygen consumption ($MVO_2$). In this study we examined the usefulness of Force-Length Area (FLA), an analogue of PVA for linear muscle, as a predictor of $MVO_2$. We measured $MVO_2$ of right ventricular papillary muscle from 15 ferrets with a polarographic myograph at 29°C during 12/min stimulation. Correlation coefficients between measured $MVO_2$ and either FLA or other indices were calculated 1) using isometric contractions only, and 2) using isometric contractions and a wide variety of shortening contractions with changing preloads, extents of shortening, and times of onset of shortening. Correlation coefficients (mean±SD) were:

| | FLA | FTI | FTI to ES | PDF |
|---|---|---|---|---|
| isometric contractions | .97±.02 | .97±.02 | .97±.03 | .96±.05 |
| isometric and shortening | .96±.01 | .89±.06 | .93±.04 | .91±.05 |

FTI: Force-Time Integral throughout a beat
FTI to ES: Force-Time Integral to End-Systole
PDF: Peak Developed Force

Thus, FLA is the best index of $MVO_2$ during contractions having widely varying mechanical conditions, although other parameters are also as reliable in isometric contractions.

26.3

**EVIDENCE OF ENHANCED CONTRIBUTION OF SARCOPLASMIC RETICULUM TO FIRST POST-REST BEAT IN FROG MYOCARDIUM AFTER OUABAIN.** **Mark E. Anderson*, Dale A. Gerasch*, Claude R. Swayze*, Irwin J. Fox. U. of Minnesota, Minneapolis, MN 55455**

**In frog (Rana pipiens) ventricular strips, ouabain causes a potentiation of the first post-rest beat peak developed tension (DT), +dT/dt max and -dT/dt max relative to control based on a percentage of pre-rest steady state values. Potentiation increases with rest duration and ouabain concentration except for $-dT/dt_{max}$. Potentiation of peak DT, $+dT/dt_{max}$, and $-dT/dt_{max}$ is partially reversed by caffeine, but not by ryanodine ($10^{-6}$M).**

**Values for 1st post-rest (60 sec.) beat after serial administration of ouabain and caffeine as % of pre-rest steady state**

| | Control | Ouabain ($1.0\text{-}1.8\times10^{-7}$M) | Caffeine (7.5-10mM) |
|---|---|---|---|
| Peak DT | 25.4±4.8 | 75.5±3.0 | 44.8±6.6 |
| +dT/dt max | 26.7±7.6 | 73.1±5.8 | 40.1±4.2 |
| -dT/dt max | 28.1±5.2 | 87.3±5.1 | 54.1±5.9 |

**A decrease in the ratio of the time (t) to peak DT of the 1st to the 5th post-rest beats was effected by addition of ouabain to the muscle bath (1.03±0.010 control and 0.984±0.007 ouabain). The rise in peak DT, ± $dT/dt_{max}$ and the decrease in time to peak DT indicate that ouabain can enhance the activity of the sarcoplasmic reticulum which can serve as both a source and a sink for contractile calcium in the first post-rest beat.**

26.4

FLUORIDE SENSITIVITY OF VENTRICULAR MYOCYTES. C.H. Greene, D.A.DeBias, D.A.DeBias*, W.L.Young*, Philadelphia College of Osteopathic Medicine, Philadelphia, PA 19131

This study was undertaken to determine whether fluoride concentrations comparable to those in fluoridated water supplies or to possible systemic concentrations following certain dental procedures could induce detectable changes in the morphology or metabolism of isolated canine ventricular myocytes. Fluoride is a known inhibitor of glycolysis. Cells in this preparation, like the myocardium of patients with chronic obstructive heart disease convert from aerobic to anaerobic metabolism via the glycolytic pathway. Myocytes were incubated for 0, 30, 60 or 90 minutes with various concentrations of fluoride with and without glucose substrate and insulin. Differences in cell length, width, and volume were measured and intracellular variables were analyzed by standard electronmicrographic morphometric techniques. Significant changes in mitochondrial and lysosomal parameters were found to be associated with fluoride exposure.

26.5

HYPOXIC STIMULATION OF Na/H EXCHANGE MEASURED BY $^{23}Na$ NMR IN PERFUSED RABBIT HEARTS. S. Anderson, P. Cala and E.Cragoe Dept. of Human Physiology, Univ. of Calif., Davis, CA 95616.

Isolated rabbit hearts were perfused with modified Krebs-Henseleit solution by the Langendorff method in a Nicolet NT-200 NMR spectrometer. Dysprosium triethylenetetramine hexaacetic acid (20mM) in the perfusate caused extracellular Na to resonate 4 ppm downfield from intracellular sodium ($Na_i$). Normoxic and hypoxic perfusates were pH adjusted to 7.35 - 7.40 after equilibration with 95% $O_2$-5% $CO_2$ and 95% $N_2$-5% $CO_2$ respectively. $Na_i$ was calculated from 5 min acquisitions by subtracting the extracellular Na peak from the spectrum and integrating the area under the upfield $Na_i$ peak. $Na_i$ was normalized by dividing the area under the intracellular peak at any time by its area during control perfusion.

| Perfusate | Normalized $Na_i$ Minutes of K+ Free Perfusion | | | |
|---|---|---|---|---|
| | 5 | 15 | 30 | 60 |
| Normoxic 100% flow | 1.2 | 3.5 | 7.5 | 6.5 |
| Hypoxic 100% flow | 4 | 13 | 20 | 25 |
| Hypoxic 25% flow | 1 | 1.2 | 4 | 15 |
| + benzamil ($5x10^{-6}$M) | 1 | 3 | 9.5 | 15 |
| + ethylisopropyl amiloride (EIPA $10^{-4}$M) | 1 | 1 | 1 | 1 |

Ouabain (2mM) had no further effect on $Na_i$. Thus inhibition of uptake by EIPA and lack of inhibition by benzamil suggest that hypoxia stimulates Na uptake via Na/H exchange. (Supported by HL21179 and CHA 84-N109A)

26.6

MYOCYTE ENLARGEMENT WITH INCREASING AGE OCCURS VIA THE SERIES ADDITION OF SARCOMERES. Aureliano Fraticelli*, Richard A. Josephson*, Robert S. Danziger*, Edward G. Lakatta, Harold A. Spurgeon. Gerontology Research Ctr., NIA, Baltimore, MD 21224

The increase in rat left ventricular (LV) weight with aging is primarily due to an increase in the size of individual myocytes. However, whether the average sarcomere length changes as well is unknown. We therefore isolated via collagenase digestion single, $Ca^{2+}$-tolerant, rod shaped, LV myocytes (Am. J. Physiol. 248:H412-H418, 1985) from 2, 8 and 24 month old rats and measured cell dimensions and slack sarcomere length (SARC) from magnified cell images (307-392 cells/age). The number of sarcomeres per cell length was computed by dividing cell length by average SARC.

| Age (mo) | No. Hearts | Cell Length (μM) | Cell Width (μm) | SARC (μM) | SARC/ Cell Length |
|---|---|---|---|---|---|
| 2 | 6 | 133.5±1.92* | 37.3±0.70 | 1.85±.008 | 72.2±1.2* |
| 8 | 8 | 146.5±2.5* | 39.3±1.10 | 1.83±.005 | 80.1±1.4* |
| 24 | 7 | 162.1±3.1* | 39.7±1.40 | 1.82±.006 | 89.0±1.9* |

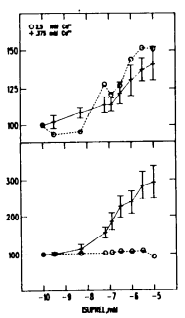
All means ± SEM, *$p<0.01$ for all comparisons.

That SARC is constant with age while cell length increases indicates a series addition of sarcomere within each cell. This may have substantial implications as to the mechanisms of myocardial contractile adaptation; for a cell from an older heart to shorten as much or as fast as a younger one each sarcomere in older cells needs to shorten less or slower than its younger counterpart.

26.7

ACTION POTENTIAL AND CONTRACTILE RESPONSES TO ISOPROTERENOL IN RAT CARDIAC MUSCLE DEPEND ON BATHING $[Ca^{2+}]$. Harold A. Spurgeon, Jeannie Y. Wei*, Edward G. Lakatta. Gerontology Research Center, NIA, NIH, Baltimore, MD 21224

Isolated rat cardiac muscle bathed in low bathing $[Ca^{2+}]$ ($Ca_o$) and stimulated at relatively low frequencies exhibits a marked inotropic response to beta-adrenergic stimulation that is highly correlated with enhanced depolarization above 40 mV of the transmembrane action potential (TAP) (Am. J. Physiol. 243:E114-E122, 1982). However, in higher $Ca_o$ the inotropic response becomes blunted. Is the augmentation of TAP also blunted? TAP and isometric contraction were measured in thin right ventricular papillary muscles stimulated at 24 $min^{-1}$ at $L_{max}$ at 29°C and bathed in physiologic saline containing either 0.375 (n=14) or 2.5 (n=5) mM $Ca_o$. Control twitch force was 1.67+.3 and 6.52 +.3 g/$mm^2$ and TAP time to -40 mV was 39+8 and 35+11 msec in the low and higher $Ca_o$ respectively. Fig. shows marked twitch potentiation in response to [isoproterenol] in lower $Ca_o$ but not in 2.5 mM $Ca_o$. The TAP response was similar in both $Ca_o$. Thus, saturation of the mechanical response occurs in the higher $Ca_o$ whilst augmentation of TAP is preserved.



## SKELETAL MUSCLE PHYSIOLOGY

27.1

CALCIUM UPTAKE BY SARCOPLASMIC RETICULUM IN HOMOGENATES OF NORMAL SKELETAL MUSCLES AND MUSCLE GRAFTS. James L. Poland, Joseph J. Feher, Franz S.F. Mong* and M. Wendy Fay*. Dept. of Physiology and Biophysics, Medical College of Virginia, Va. Commonwealth Univ., Richmond, VA 23298

Oxalate-supported calcium uptake by sarcoplasmic reticulum (SR) was studied in homogenates of normal muscles and muscle grafts. The calcium uptake exhibited a brief, fairly linear period followed by a non-linear course. The initial and more linear calcium uptake was used to measure the velocity of calcium uptake. During the non-linear phase, typically used to measure the calcium loading capacity, the addition of EGTA caused a rapid diminution in the SR calcium load. This rapidly releasable calcium could be due to the dissolution of calcium oxalate crystals externalized by SR vesicles that have ruptured. It is debatable if this rapidly releasable calcium is part of the true calcium uptake capacity. The grafts studied were autografted extensor digitorium longus (EDL) muscles. Some EDL grafts were "overloaded" by partial extirpation of synergistic muscles while others were made to work less by denervation of their antagonistic muscles. Contralateral EDL grafts served as controls. The velocity of calcium uptake and the calcium uptake capacity (excluding the rapidly releasable calcium) were similar in all groups except the overloaded EDL grafts. These grafts exhibited a modest decrease in the velocity and the capacity for calcium uptake, suggesting that "overloading" during the entire period of regeneration could have detrimental effects.

27.2

VASODILATION IN SKELETAL MUSCLE PRODUCED BY METABOLIC BLOCKADE WITH SODIUM MONOFLUOROACETATE. P.S. Clifford, J.R. Coast and R.L. Johnson Jr. Pulmonary Res. Div., Dept. Int. Medicine, Univ. of Texas Health Science Ctr., Dallas, TX 75235.

Sodium monofluoroacetate (MFA) which competitively binds the Kreb's cycle enzyme, aconitase, has been shown to produce vasodilation only in the heart and in the diaphragm. We hypothesized that failure to produce vasodilation in other beds was a result of lower metabolic rates in other tissues, i.e., the heart and diaphragm were actively working during the blockade, producing a greater concentration of vasodilator metabolites. To test this hypothesis we studied four anesthetized, spontaneously breathing mongrel dogs. Blood flow to the heart, diaphragm and both gracilis muscles was measured with radioactive microspheres. Both obturator nerves were sectioned; one was stimulated with bipolar stimulating electrodes in 5 sec trains at 3 times motor threshold voltage, 25 Hz, 0.05 msec duration, with a 5 sec rest between trains. Measurements were taken before and after 15 min of stimulation. 2 mg/kg of MFA was then injected intravenously and measurements repeated after 15 and 30 min of continued stimulation. As shown previously, MFA produced significant increases in blood flow to the heart and diaphragm. MFA produced no significant increase in flow to the resting gracilis but increased flow to the stimulated gracilis by an additional 1.048 $ml \cdot min^{-1} \cdot g^{-1}$. These findings suggest that the metabolic blockade produced by MFA results in significant vasodilation only in working muscle.

27.3

ROLE OF NON-WORKING MUSCLE ON BLOOD METABOLITES, ION AND ACID-BASE STATE DURING CYCLING EXERCISE. M.I. Lindinger*, G.J.F. Heigenhauser, R.S. McKelvie*, N.A. White* and D.S. Ward*. Dept. of Medicine, McMaster University, Hamilton, Ontario L8N 3Z5, Canada

Eight healthy males with brachial artery and antecubital vein catheters performed four 30s bouts of maximum isokinetic cycling exercise, with a 4 min rest between each exercise bout (EB); 5 subjects had biopsies taken from the non-working deltoid muscles. A-V differences across the arm showed significantly increased net uptakes of lactate (La-), K+, Na+, Cl-, metabolic H+ and glycerol and a large net release of HCO3- during exercise. Muscle glycogen contents were elevated above control values at 25 min recovery. There was no blood volume shift across the arm during exercise and recovery. Intracellular contents of Na, Cl, K, and Mg increased in the arm during exercise. In recovery there was a significant reduction in plasma and intracellular K+, and Na+ decreased to resting values. In contrast, intracellular Cl continued to increase into 25 min post-exercise, suggesting a possible anion exchange (Cl/HCO3-) across the sarcolemma. We conclude that during heavy work the non-working muscles are not inactive but that they play a major role in "buffering" acid-base, ionic and metabolic disturbances.

Supported by the Medical Research Council and the Ontario Heart and Stroke Foundation.

27.4

REPERFUSION INJURY IN SKELETAL MUSCLE. K.B. Faust,* J. Vinten-Johansen, J.H. Meredith.* Wake Forest University Medical Center, Winston-Salem, NC 27103

Extended injury with reperfusion following ischemia has been reported in several tissues, but has not been well defined in skeletal muscle. Using an in situ gracilis preparation, muscle was made totally ischemic for 4 hr, then reperfused with blood for 1 hr. Tissue ATP, calcium (Ca), and $H_2O$ content were measured before ischemia, at the end of ischemia, and after 5 min and 1 hr of reperfusion. $MVO_2$ was measured before ischemia and after 5 min and 1 hr of reperfusion. Four hours of ischemia decreased ATP from 38.9 ± 8.9 to 4.4 ± 0.8 nmol/mg protein, and reperfusion failed to restore ATP levels. In fact, ATP was lower at 1 hr (5.6 ± 2.1 nmol/mg protein) than at 5 min (10.04 ± 3.3 nmol/mg protein) of reperfusion (not significant). Tissue Ca did not increase after ischemia (2.67 ± 0.6 vs. 2.34 ± 0.5 mg%), but increased to 3.91 ± 0.6 mg% at 1 hr of reperfusion. Muscle $H_2O$ content did not increase after ischemia (76.3 ± 1.75 vs 76.8 ± 0.8%), but increased significantly after 5 min of reperfusion to 81.02 ± 1.1%. $MVO_2$ increased significantly over control after 5 min of reperfusion (0.51 ± 0.1 vs 1.54 ± 0.3 ml $O_2$/min/100 gm tissue) and then fell below control after 1 hr reperfusion to 0.3 ± 0.08 ml $O_2$/min/100 gm tissue (p=0.08). These findings suggest that progressive cellular injury occurs during reperfusion of ischemic skeletal muscle.

27.5

**RECOVERY OF TETANIC TENSION IN PARTIALLY DENERVATED RAT SOLEUS.** G.J. Herbison, M.M. Jaweed, J.F. Ditunno and S. Jeffkin. Dept of Rehabilitation Medicine, Thomas Jefferson University, Philadelphia, PA 19107

Partial denervation of muscle by removal of spinal nerve(s) causes terminal regeneration of the intact axons leading to peripheral reinnervation of the denervated muscle fibers. The extent of muscle recovery is dependent on functional maturity of newly formed synapses. Nerve-evoked tetanic tension is a quantitative measure of these synapses. Two groups (n=6-10) of 8 wks old (200-225 g) male Sprague-Dawley rats underwent unilateral $L_5$-neurectomy; whereas the two normal groups of the same age were kept as sham-operated controls. One group each of the normal and the $L_5$-neurectomized animals was evaluated in situ for parameters of isometric twitch (P) and tetanic ($P_o$) tensions of the soleus at 35-36°C at 3 and 12 wks, post-denervation. The absolute $P_o$ ($\bar{X}$±SD) values of the normal animals at 3 and 12 wks were 203±6g and 180±55g, respectively. The partially denervated soleus muscles at 3 and 12 wks were 146±46g and 132±45g, respectively. These data indicated that the recovery of rat soleus $P_o$ after $L_5$-neurectomy is not complete and it may require as long as 6 months for total recovery.

27.6

EXPRESSION OF EARLY AND LATE EMBRYONIC MYOSIN HEAVY CHAIN ISOFORMS IN THE DEVELOPING CHICKEN. R. Van Horn* and M.T. Crow. Department of Biology, University of Houston-University Park, Houston, Texas 77004

In many animals, different skeletal muscle myosin heavy chain (MHC) isoforms are expressed within the same muscle at different stages in its development. In the chicken, expression of such developmental isoforms occurs during the embryonic, posthatch, and adult stages of many fast-twitch skeletal muscles. In this report, we demonstrate that different fast MHC isoforms are also expressed at different times in embryonic development. Specifically, we show that different fast MHC isoforms are expressed by early embryonic muscles during the period in which primary generation fibers are formed and by late embryonic muscles during the period of massive limb growth and secondary generation fiber formation. The identification of these isoforms is based on differences in the peptide banding patterns of the isolated MHCs and on their differential reactivity with different fast MHC monoclonal antibodies. In ovo, the transition from early to late embryonic MHC isoform expression is blocked by agents that disrupt functional neuromuscular contacts, such as d-tubocurarine. Nonetheless, late embryonic MHC isoforms are expressed by muscle cells in culture that have differentiatied in the complete absence of nerves or neuromuscular contacts. Since muscle cell cultures established from early embryonic myoblasts do not express the late embryonic MHC isoforms, it is possible that the expression of early and late MHC isoforms is, in fact, preprogrammed among early and late skeletal muscle myoblasts. In ovo, the nerve controls the transition in these isoform types by regulating either the appearance of late myoblast populations or their differentiation. (Supported by NICHHD grant #20710)

## HYPERTENSION

28.1

Cardiovascular effects of cysteine and methionine supplemented diets in the Borderline Hypertensive Rat (BHR). R.H. Cox *, J.E. Lawler and J.T. Smith. University of Tennessee, Knoxville, TN 37996.

Both epidemiological and experimental observations suggest a relationship between the sulfur amino acids and cardiovascular function. Smith and colleagues have shown that 15% of casein diets supplemented with .505% cysteine instead of .625% methionine result in a number of metabolic and cellular changes including a decrease in opiate and beta-adrenergic receptors. These changes have immediate implications for the regulation of blood pressure. We report here the results of a pilot study which examined the effects of these two diets on blood pressure. Twelve $F_1$ female offspring of SHR x WKY matings were divided into cysteine and methionine groups at 9 months of age. Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure were recorded through an arterial cannula for 1 hour in the home cage after 21 days on the diets. The lowest measurements for a continuous 5 min block were used to compute mean values. The results ($\bar{x}$ ± S.D.) are shown below:

| | Cysteine | Methionine |
|---|---|---|
| HR | 350 ± 21.7 | 331 ± 15.6 |
| SBP | 160 ± 6.1 | 151 ± 4 * |
| DBP | 108 ± 4.3 | 101 ± 6.9 + |

* p< .05, + p< .1

No significant differences in bodyweight were noted. The mechanisms responsible for this effect are not clear but may be related to alterations in adrenergic and/or opiate receptor function.

28.2

**$\alpha_1$-Adrenoceptor Blockade (3 days) Decreases Sodium and Water Excretion in Rats.** D.D. Smyth*, D. E. Blandford* and S.B. Penner*. (Spon. D. Bose) Dept. Pharmacology and Internal Med. U. of Man. R3E 0W3.

Renal $\alpha_1$-adrenoceptor stimulation increases sodium and water reabsorption. However, prazosin (Prz) treatment ($\alpha_1$-blockade) is also suggested to increase sodium and water reabsorption. We therefore studied the effect of Prz (3 days; .15 mg/ml Prz in drinking water) on sodium and water excretion. Under anaesthesia (nembutal) the left kidney was exposed, the ureter cannulated (PE50) and a 31 gauge needle advanced into the renal artery for vehicle infusion (.0137 ml/min). A mild diuresis was induced by iv saline (.097 ml/min). The dose of Prz (3 days) attenuated (p<.05) the pressor response to phenylephrine but not clonidine. Prz produced a modest decrease in blood pressure (116 ± 13 vs 99 ± 3 mmHg) and increased creatinine clearance (1.5 ± .3 vs. 2.8 ± .2 ml/min). However, 3 days of Prz decreased (p<0.5) urine volume (24.6 ± 2.5 vs. 10.5 ± .6 ul/min) and urine sodium excretion (4.7 ± .7 vs. 1.7 ± .5 uEq/min) but not potassium (3.0 ± .3 vs 3.4 ± .2 uEq/min) excretion. These results indicate that chronic $\alpha_1$-adrenoceptor blockade is associated with an antinatriuresis. (Supported by MRC and Man. HF.)

28.3

Renal $\alpha_2$-Adrenoceptor Blockade and Sodium Excretion in Rats. D. Blandford*, D.R. Jones* and D.D. Smyth. (SPON: D. Bose). Dept. Pharmacology and Internal Medicine, U. of Manitoba.

The effect of renal $\alpha_2$-adrenoceptor blockade on sodium excretion has been variable. We therefore evaluated the effect of intrarenal yohimbine (Yoh) at various levels of diuresis established by iv infusion of saline at .025 or .097 ml/min. Under anesthesia (nembutal) the left kidney was exposed, the ureter cannulated (PE50) and a 31 gauge needle advanced into the renal artery for infusion of vehicle or Yoh (.0137 ml/min). At .097 ml/min, Yoh (.01 mg/Kg/min) decreased urine volume (25 ± 2 vs 18 ± 2 ul/min) and sodium excretion (4.7 ± .6 vs. 3.2 ± .4 uEq/min). Potassium excretion (3.0 ± .3 vs. 3.3 ± .3 uEq/min) and creatinine clearance (1.5 ± .3 vs 2.0 ± .3 ml/min) were not affected. At an infusion rate of .025 ml/min, Yoh failed to decrease urine volume and sodium excretion. Similarly, at .097 ml/min in rats treated with 3 days of prazosin to decrease urine volume and sodium excretion similar to the .025 ml/min group, Yoh again failed to alter urine volume and electrolyte excretion. These results indicate the effect of renal $\alpha_2$-adrenoceptor blockade (Yoh) may depend on the baseline level of sodium excretion. (Supp. by MRC).

28.4

ENHANCEMENT BY BRADYKININ OF THE HYPOTENSIVE AND DIURETIC BUT NOT THE NATRIURETIC ACTIONS OF ATRIAL NATRIURETIC FACTOR. D.W. Zeigler*, G.C. Awah*, C.N. Zeigler*, and M.L. Kauker. Univ. of South Dakota, Vermillion, SD 57069.

The effect of bradykinin infusion on the hypotensive, diuretic and natriuretic actions of atrial natriuretic factor (ANF) was determined in normotensive, anesthetized rats (n=8). Mean arterial pressure (MAP), urine flow ($\dot{V}$) and urinary sodium excretion ($U_{Na}\dot{V}$) were measured. Saline was infused throughout the experiment at a rate of 0.04 ml/min. Bradykinin infusion (0.2 µg/kg/hr) was begun after a control response to ANF was recorded. A bolus dose of ANF (0.25 µg, iv) was injected after 10 min of saline or bradykinin infusion. Urine was collected for 5 min and the maximal hypotensive response during the first 2 min following ANF was recorded. The results are as follows:

| | | MAP (mmHg) | $\dot{V}$ (µl/min) | $U_{Na}\dot{V}$(µEq/min) |
|---|---|---|---|---|
| Control | Initial | 122 ± 4 | 9.4 ± 1.7 | 0.81 ± 0.24 |
| | Δ ANF | -2 ± 2 | +11.2 ± 4.9 | +1.3/ ± 0.50 |
| Bradyk. | Initial | 114 ± 4* | 21.7 ± 6.2* | 2.20 ± 0.70* |
| | Δ ANF | -14 ± 3* | +23.9 ± 0.3* | +1.30 ± 0.50 |

ANF injected during bradykinin infusion significantly lowered MAP and doubled $\dot{V}$. However, increases in $U_{Na}\dot{V}$ with ANF were not significantly greater during bradykinin infusion. The results indicate enhanced hypotensive and diuretic responses to ANF by bradykinin infusion, without an effect on natriuresis.

28.5

THE EFFECT OF SALT ON THE PREGNANCY OF SPONTANEOUS HYPERTENSIVE RATS (SHR). M.C. Rice, R. Crowell, S.S. Cardoso*. LeMoyne-Owen Coll., Blackburn Coll. & Univ. of Tenn. 38163.

For almost a century, the participatory role of sodium in the pathogenesis of essential and/or pregnancy induced hypertension has remained controversial. To determine the effect of high sodium diets on gestational processes, three groups of pregnant spontaneously hypertensive rats were studied. One group (Group I) of SHR was "pretreated" with salt (saline 1% replacing water ad lib) for 3 weeks before mating, the second group was started on salt at the time of mating (Group II) and a third group was maintained on water (Group III). High sodium diets were maintained through delivery. Significantly greater elevations of blood pressures (through delivery), occured in the pretreated group when compared with animals given salt after mating and/or control rats maintained on water. At one day before delivery the blood pressure were 167±6, 148±8.5 and 110±2.5 respectively for Groups I, II and III. Adverse effects of salt on fetal growth and development were also observed, with greater morbidity and mortality occuring among pretreated animals. Birth weight for pups in Groups I, II and III were 4.78±.1, 5.06±.09 and 5.8±0.2 respectively. Mortality and liter sizes were also numerically higher in Group I as compared to Groups II and III. The results suggest that high sodium diets adversely influence both the blood pressure of the dams and the growth and development of their pups.

28.6

HIERARCHY OF BLOOD PRESSURE REGULATION IN CONSCIOUS DOGS. Paul H. Brand, Steven L. Britton, and Patricia J. Metting, Medical College of Ohio, Toledo, Ohio, 43699.

The effect on mean arterial pressure (MAP) of sequential blockade of the major pressor systems was studied in 3 conscious, resting dogs in the hydrated state and after 48 hrs dehydration. After control measurements, hexamethonium (20 mg/kg, iv) was given to block autonomic ganglia. Thirty min later, the vasopressin (AVP) antagonist $d(CH_2)_5$TyrMeAVP (AVPA, 10 µg/kg, iv) was given followed 30 min later by captopril (1 mg/kg, iv) to block angiotensin II formation. In subsequent experiments, the order of administration of AVPA and captopril was alternated. Results are summarized in the table below. Hexamethonium caused little change in MAP. When the autonomic nervous system was blocked, MAP was maintained near control levels by both the renin-angiotensin system and AVP. Dehydration increased the contribution of AVP to the support of MAP.

| | MAP, mm Hg (N=3) | |
|---|---|---|
| | Hydrated | Dehydrated |
| Control | 93 ± 3 | 89 ± 6 |
| Hex | 88 ± 5 | 90 ± 0.3 |
| AVPA | 78 ± 4 | 67 ± 1 |
| Captopril | 59 ± 3 | 49 ± 5 |
| Control | 92 ± 7 | 93 ± 6 |
| Hex | 94 ± 6 | 89 ± 4 |
| Captopril | 85 ± 3 | 80 ± 4 |
| AVPA | 70 ± 7 | 50 ± 5 |

Supported by NIH grant HL32899.

28.7

ANALYSIS OF ANGIOTENSIN II-IMMUNOREACTIVITY IN RAT TISSUES BY HPLC. Preenie DeSilva*, Robert R. Smeby, Ahsan Husain*. Research Inst. of the Cleveland Clinic, Cleveland, Oh 44106

We describe a method which allows documentation of the octapeptide hormone angiotensin II (Ang II) and all of its immunoreactive (ir) fragments in tissues. Tissues were homogenized in 20 vol 0.18 M HCl/EtOH (1:3) at 4°C. The neutralized, 2200xg supernatant was dried and applied to a $C_{18}$ Sep-pak cartridge in .1% trifluoracetic acid (TFA). The cartridge was washed with 10 ml .1% TFA and 10 ml 10% $CH_3CN$, .1% TFA. Ang II-ir was eluted with 10 ml 30% $CH_3CH$, .1% TFA,dried and used for direct RIA or RIA-HPLC analysis. Recovery of Ang II through the procedure was > 75±6%. Ang II-ir levels in normal rat plasma and adrenal were 31±8 pg/ml and 2700±120 pg/g, respectively. Uterine Ang II-ir levels were more variable (90 to 350 pg/g). Ang II-ir was analyzed on a Nova-Pak $C_{18}$ column (Waters) using a 12 min gradient between 89% buffer A (25 mM $PO_4$ pH 7.6; 5% $CH_3CN$) in buffer B (95% $CH_3CN$) and 32% buffer A in Buffer B using curve 7 (Waters gradient controller) at a flow rate of 1.5 ml/min. 0.1 min fractions were collected and Ang II-ir assessed by RIA. Retention times for Ang II, Ang III, hexa- and pentapeptide were 7.9, 10.2, 10.9, 9.4 min respectively. Ang II antisera showed 100% crossreactivity with Ang II, Ang III, and the C-terminal Ang II hexa- and pentapeptides, but < 0.05% with other Ang II fragments. Percentage of Ang II, Ang III, Ang II hexa- and pentapeptides respectively were: 76, 16, 5, 3 in adrenal; 68, 10, 11, 11 in uterus; and 64, 3, 11, 22 in plasma. This data represents the first documentation of Ang II and all of its immunoreactive fragments in tissue. Supported by NIH HL 6835

28.8

CLONIDINE ATTENUATES PRESSOR EFFECT OF INTRACEREBROVENTRICULAR ANGIOTENSIN II (AII) IN CONSCIOUS SHEEP. B.A. Breuhaus and J.E. Chimoskey, North Carolina State University, Raleigh, NC 27606 and Michigan State University, East Lansing, MI 48824-1101.

Nine conscious sheep chronically prepared with catheters in their carotid arteries, jugular veins (IV), and lateral cerebral ventricles (IVT) were used to test the contribution of central alpha$_2$ antagonism to the pressor response to central AII. This was done by comparing arterial pressure (AP), heart rate (HR), and vasopressin (AVP) responses to IVT infusion of AII by itself (50 ng/kg/min for 30 min) to those of IVT infusion of AII after pretreatment with the alpha$_2$ agonist clonidine (CLO, 1 + 0.5 µg/kg IV). In other experiments, IVT infusion of AII was also performed after adrenoceptor blockade with propranolol (PROP, 1 mg/kg IV) and phentolamine (PHENT, 1 mg/kg IV).

| | Cntl [a] | AII | Cntl | CLO AII | Cntl | PROP PHENT AII |
|---|---|---|---|---|---|---|
| AP(mmHg) | 86 | 112** | 87 | 99**++ | 87 | 98**++ |
| HR(bpm) | 79 | 76 | 84 | 67**+o | 78 | 81 |
| AVP(pg/ml) | 0.63 | 4.40* | 2.04 | 7.25* | — | -- |

a Cntl = Control * p<.05 re Cntl ** p<.01 re Cntl
+ p < .05 re AII ++ p<.01 re AII o p<.05 re PROP + PHENT +AII

Both CLO and peripheral adrenoceptor blockade reduced the pressor response to IVT AII in conscious sheep by nearly 50%. CLO also caused HR to fall in response to IVT AII. The residual increase in AP in response to IVT AII after CLO may be caused by leakage of AII into the periphery, by increased plasma AVP levels, or by some combination of the two. Supported by HL30239, HL06840, and HL37085.

28.9

RECEPTOR MEDIATED VASCULAR RELAXATION AND CYCLIC GUANOSINE MONOPHOSPHATE IN SHRSP. Y. Otsuka*, W.E. Lockette and O.A. Carretero, Hypertension Research Division, Henry Ford Hosp., Detroit, MI 48202

We have previously reported that aortae from renovascular 1K-1C, DOCA, and coarctation hypertensive rats had decreased vascular relaxation and decreased cyclic guanosine monophosphate (cGMP) in response to endothelium-dependent and endothelium-independent vasodilators. We determined the vascular relaxation and cGMP levels in response to acetylcholine (Ach) and atrial natriuretic factor (ANF) in aortae from spontaneously hypertensive stroke prone rat (SHRSP) and age-matched Wistar-Kyoto rat (WKY). Relaxation to Ach and ANF were markedly reduced in phenylephrine (PE) contracted isolated aortae from SHRSP compared to WKY. Ach caused a significant increase in cGMP only in WKY. cGMP levels in ANF-treated aortae were not different between SHRSP and WKY. These data suggest that vascular relaxation induced by both receptor mediated endothelium-dependent and endothelium-independent vasodilators is attenuated in SHRSP; however, cGMP induced by a receptor mediated endothelium-independent vasodilator is not attenuated in SHRSP.

| | Relaxation (%) | | | cGMP (pm/g wet tissue) | | | |
|---|---|---|---|---|---|---|---|
| | Ach ($10^{-5}$M) | ANF ($10^{-8}$M) | ANF ($10^{-7}$M) | PE only | Ach ($10^{-5}$M) | ANF ($10^{-8}$M) | ANF ($10^{-7}$M) |
| WKY | 69±5 | 98±1 | 100±0 | 121±19 | 215±22 | 322±20 | 410±44 |
| SHRSP | 13±4* | 72±5* | 96±3 | 127±9 | 152±9* | 262±21 | 336±35 |

($n \geq 5$. *P<.05, supported by AHA of MI and NIH grant HL 28982)

28.10

INCREASED ELECTROGENIC PUMPING AND ELEVATED SODIUM ACTIVITY IN SKELETAL MUSCLE CELLS FROM HYPERTENSIVE STROKE PRONE RATS. Gregory D. Goggins* and George D. Webb. Univ. of Vermont, Burlington, VT 05405

To test the hypothesis that cellular Na transport is altered in hypertensive animals, a conventional and a Na-sensitive microelectrode were used. After measurements of membrane potential and Na activity in several fresh skeletal muscle (EDL) cells, the bath was changed from the standard 5 mM K to zero K. Cells from WKY control rats immediately hyperpolarized, whereas the SHR-stroke prone immediately depolarized, suggesting a more highly electrogenic Na-K pump in the SHR-SP rat cells. Meanwhile, the contralateral muscle was loaded with Na by exposure to zero K for 6 hours. The means of the Na activities (mM) for six SHR-SP vs six age-matched WKY rats (±S.D.) were: For fresh cells: 9.0 (±0.9) vs 6.4 (±2.1), p=.021. For Na-loaded cells: 47.5 (±6.0) vs 33.7 (±6.5), p=.0033. Fresh skeletal muscle cells from hypertensive stroke prone rats have 41% more Na than the normotensive controls. During loading, the SHR-SP rat muscle cells gained 38.5 mM and the WKY cells gained 27.3 mM, indicating that the hypertensive cell membranes are more permeable to Na. This can account for the observed higher intracellular Na activity measured in fresh cells, which in turn will stimulate faster Na-K pumping and make the pump more electrogenic, as was observed. In vascular smooth muscle cells similar changes would result increased intracellular Ca and tension development, thus raising blood pressure.

## CEREBRAL CIRCULATION

29.1

DOSE DEPENDENT POSTRADIATION CHANGES IN PRIMATE BLOOD PRESSURE AND CEREBRAL BLOOD FLOW. C. D. Forcino*, T. J. Cerveny and L. G. Cockerham. Physiology Department, Armed Forces Radiobiology Research Institute, Bethesda, MD 20814-5145.

High doses (100 Gy) of ionizing radiation produce marked hypotension in the primate, often accompanied by decreased regional cerebral blood flow (rCBF). To determine if these radiation-induced phenomena occur at much lower doses, sub-human primates were exposed to various levels (6.25-100 Gy) of whole-body, gamma radiation. Hippocampal rCBF (via hydrogen clearance) and systemic mean arterial blood pressure (BP) were determined simultaneously every 10 min for 30 min before and 60 min after exposure. Data obtained from the 5 groups (n = 6/group) of radiated primates indicated a reduction in BP for each of the 5 doses employed. Only the 6.25 Gy dose did not produce a decrease in rCBF. Both BP and rCBF data at 10 min postradiation suggest a quantal response to a gamma radiation dose between 12.5 and 25 Gy, with the BP precipitously dropping to a value approximately 30% of the preradiation level and the rCBF to 40% for doses of 25 Gy or greater. Both parameters display a triphasic response with radiation doses of 25 Gy or greater. Using the data points obtained for both parameters at 30 min postradiation, dose-response curves may be constructed to give excellent biological indications of the exposure level, an exceptional tool for the prognosis and treatment of acute radiation injury.

29.2

ROLE OF POLYAMINES IN THE CEREBRAL MICROVASCULAR RESPONSE TO ISCHEMIA. Scot L. Harper, William V. Wojciechowski, and Patsy C. Covey, University of South Alabama, Mobile, AL 36688

Cerebral ischemia/reperfusion is characterized by a combination of vasodilation and increased microvascular permeability leading to edema formation and the possiblity of infarction. Recent evidence indicates that polyamines derived from ornithine (putrescine, spermidine, and spermine) are present following cerebral ischemia. We evaluated the effects of topically applied polyamines on microvascular tone and permeability in the anesthetized Mongolian gerbil, using in vivo microscopy. The mean ± SE $ED_{50}$ values were as follows (-log M): putrescine, 6.55±0.14; spermidine, 7.16±0.19; spermine, 6.19±0.17. These doses are consistent in magnitude with published values of post-ischemic brain polyamine content. The above concentrations, when constantly suffused in buffered artificial CSF over a period of 30 min or more, result in nearly immediate (<1 min) cerebral arteriolar dilation (23% increase), followed later by increased capillary and venular permeability and plasma protein extravasation. There is a significant time lag (>15 min) between these dilator and permeability effects. Microvascular polyamines known to accumulate following ischemic insult may, in part, mediate processes culminating in vasogenic edema formation. (Supported by NIRA HL-33456 and a Grant-in-Aid from the Alabama Affiliate of the American Heart Association.)

29.3

ENDOTHELIUM-DEPENDENT RESPONSES OF CEREBRAL ARTERIES FOLLOWING ISCHEMIA AND REPERFUSION IN CATS. W.G. Mayhan, S. Amundsen, F.M. Faraci, and D.D. Heistad. CV Center and VA Hosp., Univ. of Iowa Coll. of Med., Iowa City, IA 52242

Acute episodes of cerebral ischemia followed by reperfusion produce disruption of the blood-brain barrier and may damage cerebral endothelium. Our goal was to determine whether responses of cerebral arteries (179±6 μm; mean±SE) to agonists that may release endothelium-derived relaxing factor (EDRF) are altered following cerebral ischemia. Ischemia was produced for 5 min by clamping the brachiocephalic and subclavian arteries followed by inflation of a neck cuff. We studied responses to topical application of agonists which release EDRF (serotonin and acetycholine) and EDRF-independent agonists (angiotensin and adenosine) before and 20-30 min following cerebral ischemia, when baseline diameter had returned to control levels. Values (% change in diameter):

| | Control | Reperfusion |
|---|---|---|
| Serotonin (1μM) | -17±2 | -18±3 |
| Angiotensin (0.1μM) | -22±3 | -27±5 |
| Acetylcholine(5μM) | +16±2 | +2±1 (p<0.05 vs control) |
| Adenosine (100μM) | +17±2 | +18±2 |

These results suggest that constrictor responses are preserved following ischemia and reperfusion, but endothelium-dependent dilatation is impaired. We speculate that impaired endothelium-dependent dilatation may contribute to impaired reperfusion after cerebral ischemia.

29.4

SEGMENTAL VASCULAR RESPONSES TO ACUTE HYPERTENSION IN CEREBRUM AND BRAIN STEM. F.M. Faraci, W.G. Mayhan, and D.D. Heistad. Internal Medicine and CV Ctr., VA Medical Ctr. Univ. of Iowa College of Medicine, Iowa City, IA 52242

Large arteries account for a large portion of total resistance in brain. During increases in aortic pressure, the brain stem (BS) autoregulates more effectively than the cerebrum (C). We tested the hypothesis that resistance of large arteries (LAR) is greater and thus increases in pial artery pressure (PAP) are less in BS than C during acute hypertension. We measured blood flow (microspheres) and PAP (servo-null) in pial arteries (∿170μm) of anesthetized cats, and calculated LAR and small vessel resistance (SVR) in C and BS. Values (mean ± SE) during control (CON) (aortic pressure ∿90 mmHg), moderate hypertension (MH) (∿130 mmHg), and severe hypertension (SH) (∿200 mmHg) (*=P< 0.05 vs cerebrum):

| | Cerebrum | | | Brain Stem | | |
|---|---|---|---|---|---|---|
| | CON | MH | SH | CON | MH | SH |
| Flow | 29±2 | 31±2 | 124±35 | 28±2 | 31±4 | 54±8* |
| PAP | 54±8 | 83±6 | 122±3 | 71±6* | 113±5* | 169±6* |
| LAR | 1.5±0.2 | 1.6±0.1 | 0.8±0.2 | 0.9±0.1* | 0.7±0.1* | 1.0±0.2 |
| SVR | 1.7±0.2 | 2.6±0.3 | 1.3±0.3 | 2.9±0.4* | 3.9±0.4* | 3.9±0.6* |

Thus, 1) LAR is greater in C than BS under control conditions, 2) PAP is higher in BS than C during CON, MH and SH, and 3) during SH, both LAR and SVR decrease passively in C and both are maintained in BS. These data suggest that more effective autoregulation in BS than C is due to greater resistance of small, not large, vessels.

29.5

DEFEROXAMINE AND CEREBRAL ISCHEMIA. R. Christian Crumrine* and Joseph C. LaManna. Case Western Reserve University, Cleveland, Ohio 44106

CNS damage secondary to cardiac arrest is produced both during the ischemic event and during reperfusion. Reperfusion injury may be amenable to therapeutic intervention. Since lipid peroxidation initiated by $Fe^{+2}$ catalyzed reactions might be responsible for reperfusion injury, we used deferoxamine, an iron chelator, in our double balloon occlusion model of cerebral ischemia in dogs. If $Fe^{+2}$ is unavailable, these reactions might be reduced or eliminated, thus facilitating the return of normal cellular function.

Six dogs were subjected to 15 min of complete cerebral ischemia. Three received deferoxamine (100 mg/kg) immediately post occlusion. Microsphere-determined cerebral blood flows were taken pre-occlusion and at 1, 3, 6, and 24 hours post occlusion. Arterial blood plasma was assayed for lactate levels before and after occlusion. A 7 day neurological exam was performed on surviving animals.

The three control dogs showed delayed hypoperfusion, whereas the treated dogs did not. While 1 control dog survived 7 days, none of the treated dogs did. The treated dogs had a high plasma lacate level throughout the first 3 hours, while the control dogs showed a steady decline. We, therefore, find no evidence to indicate that deferoxamine can improve survivability or improve neurological recovery after a 15 min ischemic insult to the brain.

29.6

PROTECTIVE ACTION OF THE CALCIUM ANTAGONIST FLUNARIZINE ON CEREBRAL ISCHEMIA. Owen S. Bunnell*, Rita L. Saldahna*, Arthur E. Kopelman* and Thomas M. Louis. Depts. of Anatomy and Pediatrics, School of Medicine, East Carolina University, Greenville, NC 27834

The calcium antagonist flunarizine was studied to assess its potential protective effect against cerebral ischemia. Sixty-eight female mongolian gerbils (avg. wt. 50±2 grams) were randomly assigned to one of three treatment groups: control (no treatment, n=22), flunarizine (400 μg/kg, IP, n=24), or vehicle (200g/L ethanol, 170g/L polyethylene glycol, 2g/L sodium citrate, and 0.3g/L citric acid in distilled water, IP, n=22). Drugs were given 15 min. prior to surgery. Each gerbil then underwent a 15 min. bilateral carotid artery occlusion. Following the occlusion, the animals were placed in an oxygen chamber and administered 100% oxygen for 1 hour. Efficacy of treatment was assessed in terms of mortality and total recovery. There was no significant difference between flunarizine and the vehicle in terms of recovery and mortality; however, there was a reduction in mortality in both the flunarizine and vehicle groups as compared to controls. Flunarizine improved recovery (p=.02) and reduced mortality (p=.02) as compared to the controls. However, there was no significant difference between the vehicle and control groups in terms of recovery. The results of this study indicate that the calcium antagonist flunarizine produces improvement in neurological recovery following cerebral ischemia, and that the vehicle may possibly augment the effect of flunarizine.
This research was sponsored by a grant from The United Way to R.L. Saldahna.

29.7

NIMODIPINE BEFORE OR AFTER CEREBRAL ISCHEMIA IMPROVES OUTCOME. T.M. Louis, O.S. Bunnell*, R.L. Saldahna*, M.D. Cruze*, and A.E. Kopelman*. Depts. of Anatomy and Pediatrics, School of Medicine, East Carolina University, Greenville, NC 27834

We studied the effect of nimodipine, a calcium entry blocker, on recovery rate and survivability following cerebral ischemia. Two ischemia models were used. In model one, gerbils were either given Nimodipine 15 mins. prior to surgery (400 μg/kg, IP, n=20) or received no treatment (controls, n=14). Gerbils then underwent 15 mins. bilateral carotid occlusion (CAO) followed by administration of 100% $O_2$ for 1 hr. In model two, gerbils underwent 5 mins. of bilateral CAO followed by 1 hr. of unilateral CAO. After CAO, gerbils were either given Nimodipine (400 μg/kg, IP, n=17) or received no treatment (controls n=19). Animals were assessed for stroke signs at 1, 24, 48, and 72 hrs. In animals treated prior to cerebral ischemia there was an increase in complete recovery ($p<.03$, Fisher's Exact Test), but not in survivability. In animals treated after cerebral ischemia, there was an increase in complete recovery ($p<.02$) and survivability ($p<.02$). Nimodipine improved recovery rate in both models; however, the mortality rate in gerbils treated before cerebral ischemia was not affected by Nimodipine. We conclude that Nimodipine improves recovery when given before or after cerebral ischemia.

This research was sponsored by a grant from The United Way to R.L. Saldahna.

29.8

ENDOTHELIAL MODULATION OF CEREBROVASCULAR REACTIVITY AND MEMBRANE POTENTIAL INNORMAL AND PATHOLOGICAL STATES. Shigeru Nishizawa, Takao Bun, and John W. Peterson. Massachusetts General Hospital, Boston, Massachusetts 02114

We have studied the reactivity of isolated, perfused segments of canine basilar artery to vasoactive materials applied to the lumen only in 3 preparations: Vessels (1) with healthy endothelium, (2) denuded of endothelium, and (3) excised while in a state of vasospasm after subarachnoid hemorrhage. Luminal application of serotonin ($10^{-6}$ M) causes a tonic constriction of both de-endothelialized and "spasm" vessel segments, but only a transient constriction in vessels with healthy endothelium. The same responses were observed with luminal application of low molecular weight ultrafiltrates of plasma. The endothelium-dependent vasodilator Substance-P causes no inhibition of serotonin constriction in "spasm" vessel segments. "Spasm" vessels are always slightly depolarized relative to control vessels (about -37 mV versus -45 mV). De-endothelialized control vessels are similarly depolarized, suggesting that the endothelium exerts a direct influence on cerebrovascular smooth muscle membrane potential. While spasm vessel segments possess good endothelial coverage, as seen histologically, they are apparently functionally de-endothelialized.

## REPRODUCTION; FETAL AND NEONATAL PHYSIOLOGY

30.1

Superfused Pituitary Cells:Responsiveness Exhibited by Various Estrous Stages When Stimulated with Brief LHRH Pulses. A.R. Clary*, T.A.Kellom* and J.L.O'Conner* (Spon V.B. Mahesh). Dep't of Physiology and Endocrinology, Medical College of Georgia, Augusta,GA 30912.

To better define ovulatory pituitary LHRH sensitivity, superfused pituitary cells were used to determine (1) the pulsatile LHRH responsiveness of cells from each stage of the 4d cycle,(2) the modulation of proestrous LHRH responsiveness and (3) how these observations compared for LH and FSH. Dispersed pituitaries were prepared from 60 day rats on estrus and diestrus at 0800 and on proestrus at 0800, 1500 and 1900. Superfusion columns utilized 3 pits/column. LHRH was applied as a 100ul pulse at 60 min intervals for 4h (4ng at h 1,2 & 3 and 100ng at h 4). Pulsatile responses were identified (Goodman & Karsch,Biol Reprod 1980;Reame et al,J Clin Endo Metab 1984) and a log transform was performed on the data;ANOVA followed by Tukey's HSD sought differences in estrous stages. Maximum LH responsiveness was observed as follows:estrus 0800>proestrus 1900> d1 0800>d2 0800>proestrous 1500>proestrus 0800. These studies suggest that (1) the system maintains significant in vivo LHRH response, (2) the pituitary is capable of retaining for several days its in vivo steroid priming,(3) LHRH pulse regimens which induce pulsatile LH release may not induce pulsatile FSH release and (4) in vivo circulating gonadotropin levels may be determined by modulation of responsiveness and also by availability of pulsatile hypothalamic LHRH. Supported by NIH-HD-16433.

30.2

DETECTION OF IMMUNOHISTOCHEMICAL STAINING IN A SUBPOPULATION OF RAT ADENOHYPOPHYSEAL CELLS WITH ANTISERUM RAISED AGAINST A PEPTIDE ENCODED BY A RNA COMPLEMENTARY TO HUMAN GnRH PRECURSOR PEPTIDE mRNA. T. Gorcs*, P. Gottschall*, D. Coy* and A. Arimura. US-Japan Biomed. Res. Labs., Tulane Univ., Hebert Center, Belle Chasse, LA 70037.

Peptides complementary to the mRNAs of rat GnRH Pro-Arg-Ala-Gln-Pro-Ile-Gly-Pro-Val-Leu (rHRnG), and to human GnRH precursor peptide Ala-Gly-Ala-Leu-Val-Pro-Gly-Ile-Ser-Gln-Ala-Arg-Ser-Ser-Leu-Ser (hpHRnG) were synthesized. Neither peptide bound GnRH in a detectable manner in either ELISA or radioimmunoassay using $^{125}$I-labelled GnRH. Two rabbits were immunized against each peptide. The titers of antisera were monitored by ELISA. One of the hpHRnG-immunized rabbits showed relatively high antibody titer after the first bleeding (#281) with further increase after second booster. About 10% of rat adenohypophyseal cells were stained using indirect immunofluorescence. Immunostaining was abolished by pre-incubating the antiserum with hpHRnG, but not with rHRnG or GnRH. Serum testosterone levels markedly decreased in rabbit #281. The radioreceptor assay with $^{125}$I-GnRH agonist as the ligand showed that binding of ligand with the membrane preparation for rat hypophysis and gonads was reduced by the addition of antiserum #281 in a dose-related manner, but no inhibition of binding was observed by either sera from rHRnG-immunized rabbits or unimmunized normal rabbit serum. Data presented suggest the possibility that antiserum to hpHRnG recognized GnRH receptors. Supported by NIH HD 14761.

30.3

DOES GONADOTROPIN RELEASING HORMONE-LIKE (GnRH-L) PEPTIDE EXIST IN RAT TESTIS? N. Minamino*, P. Gottschall* and A. Arimura. US-Japan Biomed. Res. Labs, Tulane Univ., Hebert Center, Belle Chasse, La 70037.

Although the existence of GnRH-L in the rat testis as a possible physiological ligand for the testicular GnRH receptor has been reported, the GnRH-L has not been isolated or characterized. We have begun a systematic survey for GnRH-L using a stable radioreceptor assay (RRA) and have demonstrated that peptidergic materials of rat testis exert receptor binding activity (RBA).

RRA was conducted using rat testis membrane preparation from isolated interstitial tissue and $^{125}$I-Buserelin (D-Ser (tBu)$^{6}$-des-Gly$^{10}$-ethylamide GnRH)(Hoechst) as the ligand. Bo/T and Kd are 16% and 1.2x10$^{-10}$M, respectively. Boiled rat testicular extracts in 2 M acetic acid were submitted to acetone precipitation followed by C-18 reverse phase chromatography which removed large proteins, salts, amines, and others. The C-18 eluate showed a displacement curve parallel to the standard in RRA. Subsequent SP-Sephadex ion exchange chromatography showed that GnRH-L was eluted only with weakly basic (SP-2) and basic materials (SP-3). The RBA of SP-3 was 3-4 times greater than SP-2. Enzymatic digestion of SP-2 and 3 by trypsin or chymotrypsin abolished RBA. Therefore, GnRH-L of rat testis are considered to be weakly basic and basic peptides. The mol wt of RBA of SP-3 was observed to be between 15,000-2,000 daltons on gel filtration with Sephadex G-50 column. No activity was detected around the elution position for GnRH. (Supported in part by NIH grant HD 14761)

30.4

LHRH AGONIST EFFECTS ON THYMUS AND BONE MARROW IN FEMALE RATS. C.M. Blacker*, K.M. Ataya*, R.T. Savoy-Moore, M.G. Subramanian. Dept. of Ob/Gyn, Wayne State Univ., Detroit, MI 48201.

We have described that LHRH agonist increased thymus, spleen, and body weights in female rats (Endocr. Soc. Mtg., Abs. 503, 1986). To investigate the mechanism, D-Leu-6, Des Gly-10-LHRH (LHRHa; 5ug/day) or saline (Ctl) was administered by continuous infusion (minipump) for 21 days to intact or ovariectomized (OVX) female rats (8/group). LHRHa rats entered persistent diestrus. Intact rats had normal cycles. Organ weights (mean + SEM) expressed per 100 g body weight (BW) and femoral bone marrow cell counts (cells/cmm) are below.

| Group | Rate BW | Thymus | Uterus | Ovary | Bone Marrow |
|---|---|---|---|---|---|
| LHRHa | 2.5 | 22.0 | 6.3 | 1.77 | 21059 |
| | ± .1 | ± 1.9 | ± .4 | ± .09 | ± 2087 |
| Ctl | 1.0 | 14.2 | 18.3 | 3.02 | 31710 |
| | ± .2 | ± 1.6 | ± 1.2 | ± .25 | ± 3049 |
| OVX LHRHa | 2.5 | 20.8 | 5.1 | | 32696 |
| | ± .2 | ± 1.7 | ± .3 | — | ± 2089 |
| OVX Ctl | 2.2 | 17.6 | 5.5 | | 32416 |
| | ± .4 | ± 1.2 | ± .3 | — | ± 1803 |

This study confirmed our previous findings of increased thymus wt. ($p<.05$), and decreased ovarian and uterine wts.($p<.005$) in LHRHa treated rats. LHRHa and oophorectomy comparably increased BW gain ($p<.005$). Bone marrow cell counts were significantly decreased in LHRHa treated intact rats ($p<.05$). Uterine and BW gain were similar in OVX and LHRHa groups, suggesting that these effects in LHRHa rats were secondary to "medical oophorectomy" induced by LHRHa. A lack of estradiol alone cannot explain the effect on the thymus, since the thymic wts. of OVX rats were significantly lower than LHRHa rats. This implies that LHRHa can act directly on the thymus.

30.5

hFSH BIOACTIVITY THROUGHOUT THE MENSTRUAL CYCLE: POSSIBLE MODULATION BY SEX STEROIDS. Vasantha Padmanabhan, J. Sonstein*, and I.Z. Beitins*, Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, MI 48109-0274.

Serum FSH bioactivity was measured by determining the Sertoli cell FSH dependent aromatase activity in four subjects. Each had a biphasic basal body temperature chart, serum immunoreactive LH levels and estradiol ($E_2$) and progesterone (P) levels within 1 S.D. of values obtained within 20 normal ovulatory control cycles in daily blood samples. Briefly, the testes of immature rats (7-10 days) were subjected to a 2 step collagenase dispersion followed by growth in DMEM; HAM's F10 (1:1) containing growth factors and .1mM MIX for 72h. The cells were then washed and reincubated in medium containing increasing doses of NIAMDD-hFSH-2 or small volumes (1 to 5 µl) of serum and 19-OH androstenedione (2.5 x 10$^{-6}$ M) for 24h. Estradiol in the medium and hFSH in serum were measured by RIA. The results of the bioactive (B), immunoreactive (I) hFSH (ng/ml) and resulting B/I ratios in 2 subjects grouped according to the days of the LH peak are:

| Phase of Cycle | Early Follicular | Late Follicular | LH Surge | Luteal | |
|---|---|---|---|---|---|
| Days | -14 to -8 | -7 to 0 | 0 | 0 to 7 | 7 to 14 |
| B FSH | 9.2 ± 1.4 | 11.3 ± 1.5 | 30.0; 43.0 | 9.5 ± 2.1 | 2.5 ± 0.8 |
| I FSH | 5.7 ± 0.5 | 3.7 ± 0.2 | 7.5; 3.3 | 3.7 ± 0.2 | 3.2 ± 0.3 |
| B/I | 1.7 ± 0.4[a] | 3.1 ± 0.4[b] | 4.0; 13.0 | 2.6 ± 0.6 | 1.1 ± 0.4[c] |

Mean ± S.D. $P < 0.05$ b vs a; $P < 0.01$ b vs c; Scheffe's t test

In conclusion: 1) B/I ratio of hFSH rises significantly during late follicular phase, 2) the bioactive hFSH peak is concordant with the LH peak, 3) during the luteal phase the B/I ratio of hFSH is low presumably due to P, 4) B hFSH is not concordant with I hFSH, 5) changes in B/I ratios are possibly modulated by changes in the steroid milieu. Source of support: NIH HD18515.

30.6

DIMINISHED METABOLIC AND VASCULAR β-ADRENERGIC RESPONSIVENESS IN ESTRADIOL BENZOATE (EB)-TREATED RATS. D.L. Kelleher and M.J. Fregly, Dept. Physiol., Univ. of Florida, Col. Med., Gainesville, FL 32610.

Earlier studies have shown that chronic treatment with EB reduced the responsiveness of heart rate, drinking and tail skin temperature (TST) to administration of the β-adrenergic agonist, isoproterenol (ISO). The objective of the present study was to assess the relationship between the ISO-induced elevations of oxygen consumption ($\dot{V}_{O2}$) and TST in adult ovariectomized (OVEX) female rats treated chronically with EB (28 ug/day) and untreated, OVEX controls. ISO (0, 10, 25, and 50 ug/kg, s.c.) elevated both $\dot{V}_{O2}$ and TST in OVEX and OVEX + EB-treated rats in a dose-related fashion. However, in both cases the response of the EB-treated group was less than controls. A regression of the integrated responses of $\dot{V}_{O2}$ vs TST for all doses of ISO administered to each group revealed significant correlations. Both slopes and intercepts of the regressions for the two groups differed significantly, suggesting a reduced TST response at a given $\dot{V}_{O2}$ for the EB-treated group. We conclude that the reduced metabolic response to β-adrenergic stimulation in estrogen-treated rats explains, in part at least, the attenuated TST responses. (Supported by grant HL 14526-13 from NIH).

30.7

MALE REPRODUCTIVE DYSFUNCTION IN THE HYPERPROLACTINEMIC RAT. D.F. Cameron*, M.J. Katovich, G. Papadi*, J. Friedman*, P. Kalra* and W.J. Millard*, Depts. of Anatomy and Cell Biology and Pharmacodynamics, University of Fla., Gainesville FL 32610.

Elevated serum prolactin is associated with infertility in females and believed to interfere with testicular function in males. To investigate the latter, hyperprolactinemia was induced in adult Wistar-Furth rats by tumor implantation and sacrificed at 1, 2, 3, 4, 5 and 6 weeks. Reproductive status was evaluated by analysis of reproductive hormones, testicular morphology, accessory sex gland weights and determination of daily sperm production (DSP). Serum prolactin and growth hormone progressively increased, accompanied by significant decreases of LH at 2 weeks, FSH at 3 weeks and serum testosterone at 4 weeks. Hormone levels remained normal in control rats. In experimental rats, testicular pathology was present, DSP was minimal at 6 weeks and accessory gland weights fell in parallel with reduced testosterone. In a second study, hyperprolactinemic rats were supplemented with testosterone and evaluated after 5 weeks. Steroid-treated rats showed higher levels of serum prolactin and GH than untreated hyperprolactinemic rats, an even greater reduction of gonadotropins, and more advanced testicular pathology. DSP was severely affected. Results indicate that elevated prolactin interferes with testicular function and that reduced testosterone does not account for the observed reproductive pathology, but in fact potentiates it via an apparent stimulation of the prolactin secreting tumor. (Supported by NIH Grant HD19742, & HD11362.

30.8

EFFECTS OF ETHANOL ON ANDROGEN RECEPTORS IN THE RAT PITUITARY GLAND. Kyung W. Chung, Department of Anatomical Sciences, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104

The present study was carried out to determine whether ethanol has an adverse effect on androgen binding to receptors in pituitary glands. Rats serving as controls were maintained on a sucrose liquid diet, whereas experimental rats were kept on an ethanol liquid diet for 5 months. Androgen binding was studied in the cytosol of pituitary glands from control and alcohol-fed rats by charcoal assay. Tissues were homogenized in TEDG (0.05M Tris, pH 7.4, 0.15 mM EDTA, 0.25 mM dithiothreitol, 10% glycerol) and centrifuged at 105,000 x g for 1 hour to obtain the cytosol fraction. Two hundred ul of charcoal-treated cytosol were incubated with increasing concentrations of testosterone-1β,2β-$^{3}$H (0.1-8nM) in the presence or absence of 500-fold excess of nonradioactive testosterone. Scatchard plot analysis of the data revealed that in pituitary glands from control animals, the mean value for the amount of androgen receptors was 15 fmol/mg cytosol protein (Kd=0.7 nM). Binding sites in the cytosol of ethanol-fed rat pituitaries decreased to 8 fmol/mg protein. No differences in Kd values was found between alcohol-fed and control subjects. Such observations suggest that ethanol exerts a suppressive effect on the level of androgen receptors and pituitary functions in general. Supported by NIAAA Grant 1 R01 AA06448-01A1.

30.9

CHARACTERIZATION OF DEHYDROEPIANDROSTERONE (DHEA) BINDING PROTEIN IN RAT LIVER. Mohammed Kalimi and William Regelson*, Medical College of Virginia, Richmond, VA 23298.

A high affinity (Kd ~2nM) [$^3$H]DHEA binding macromolecule was identified in male Sprague-Dawley rat liver cytosol. High specificity of binding for DHEA was shown by competition studies in which binding of [$^3$H]DHEA was 80-90% inhibited by unlabelled DHEA. 17β estradiol and testosterone were less effective (20-30% inhibition) while dexamethasone and progesterone were ineffective. We also found differences in specific binding of [$^3$H]dexamethasone, [$^3$H]17β-estradiol and [$^3$H]DHEA to the rat liver cytosol when the binding assays were performed using Tris-sucrose buffer pH 7.5 (10mM Tris HCl, 0.25M sucrose) containing 0.1M sodium thiocyanate. [$^3$H]Dexamethasone binding was reduced almost 50%, [$^3$H] 17β estradiol binding remained unchanged, and [$^3$H]DHEA binding increased almost 40-50% over the control in incubations containing Tris-sucrose buffer pH 7.5. No significant change in the affinity was observed between control and 0.1M sodium thyiocyanate treated samples. The results suggest a presence of high affinity and steroid specific DHEA binder in the rat hepatic cytosol.

30.10

EFFECT OF TSS(TJ-23) ON OVULATION INDUCED BY hMG (GNR 4) Takao Koyama*, Nobuyoshi Hagino, Anna Cothron*, Jong-Chaur Shieh* and Esperanza Gonzalez*, The University of Texas Health Science Center at San Antonio, Texas 78284.

Clinically TSS(TJ-23, oriental herbal medicine) has been shown to improve ovarian dysfunction in cases of ammenorrhea. This clinical evidence suggests that TSS seems to act directly on the ovaries to improve ovarian function. Therefore, we designed the following experiments: 115 Sprague Dawley immature female were treated with TSS (500mg/kg BWT in drinking water) beginning on 25 days of age and during experimental sessions. The hMG (15iu of Mochida Gonadoryl 4; GNR4 which contains 4 to 1 ratio of FSH and LH) was injected intraperitoneally on the morning of 28 days of age, and ovulation (presence of tubal ova) was examined on the morning of 29, 30 and 31 days of age. GNR4 alone induced ovulation (65%) only once on 29 days of age. TSS treatment alone caused 30% to ovulate on 31 days of age. When GNR4 was combined with TSS treatment, animals demonstrated ovulation twice; once was on 29 days of age (60% of ovulation) and again on 31 days of age (90% of ovulation). This experiment suggests that TSS treatment may accelerate the chain of events in the neuroendocrine control of ovulation thus causing more frequent ovulation. Therefore, combined treatment of GNR4 with TSS may, in the future, become an effective clinical treatment for women with ammenorrhea, luteal dysfunction and/or anovulatory syndrome. (Study was supported by Tsumura Juntendo Pharmaceutical Ltd.)

30.11

OVARIECTOMY-INDUCED MAMMARY GLAND TUBULIN POLYMERIZATION: DIFFERENCES BETWEEN PRIMIPAROUS AND MULTIPAROUS PREGNANT RATS. Robert F. Loizzi. Univ. of Illinois at Chicago, Chgo IL 60680

We have shown previously (PSEBM 173:252, 1983) that OVX-induced lactogenesis in late pregnant rats is accompanied by a partial shift of mammary gland (MG) tubulin (TU) from the free to the polymerized state, thus increasing % polymerization (P) without altering total TU content. Lactation includes further P plus an increased TU content. To determine the effects of immediate postpartum pregnancy and induced lactogenesis on MG TU status, primiparous and postpartum-mated multiparous, 18d pregnant rats underwent OVX or SHAM surgery and MGs were collected 24hr later. Both groups showed similar lactogenic responses indicated by 3-6x increases in MG lactose, the only difference being that multiparous glands contained about 50% more basal lactose than primiparous. OVX did not change the total TU content significantly in either group, nor did groups differ from each other. However, the status of the polymerized TU pools and their responses to OVX did differ. Primiparous animals after OVX had 44% more polymerized TU (7.02% vs. 10.2%) while %Ps in glands from multiparous SHAM and OVX rats were equal (13% vs. 14.7%) and about one-third higher than the primiparous OVX. The results indicate that the size of the polymerized TU pool, once increased by lactogenesis/lactation, unlike lactose content, resists returning to the lower level present during an initial pregnancy. (Supported by NIH grant HD 11601)

30.12

LOCALIZATION OF ATRIAL NATRIURETIC FACTOR (ANF) IN SPONTANEOUSLY HYPERTENSIVE AND WISTAR-KYOTO FETAL RAT HEARTS. Jane N. Scott and Lothar H. Jennes* Wright State University, Dayton, OH 45387

Atrial natriurectic factor (ANF) has been localized in atrial myocytes of all adult and newborn mammals studied to date. Thus, the present investigation was undertaken to compare the distribution of ANF in fetal hearts of spontaneously hypertensive rats (SHR) and control-strain Wistar-Kyoto rats (WKY). Hearts from SHR and WKY fetuses at 20 days of gestation were fixed in Bouin's solution, processed for paraffin sectioning and stained immunohistochemically for ANF. Myocytes containing ANF were found throughout the right and left atria of the fetal hearts. In addition ANF positive cells were observed in the fetal ventricles. The ventricular ANF cells were localized near the lumen of the right and left ventricles. ANF positive myocytes were not observed in the rest of the ventricular myocardium or epicardium. Similarly ANF positive cells were not observed in the walls of the great vessels. There were no obvious SHR-WKY strain differences in the distribution of ANF at 20 days of gestation. Since the presence of ANF in ventricles has been reported only in nonmammalian vertebrates, further studies are needed to determine whether or not the localization of ANF in the ventricles is transient and restricted to certain developmental stages. (Supported by Miami Valley Chapter of the American Heart Association MV-86-010 and MV-86-019).

30.13

U-63,557A, A Thromboxane Synthetase Inhibitor, Improves Renal and Cardiovascular Function in Ovine Pregnancy Toxemia. J.C. Keith, Jr., C.D. Thatcher,* R.G. Schaub. VPI&SU, Blacksburg, VA 24061 and The Upjohn Company, Kalamazoo, MI 49001.

Ovine pregnancy toxemia (OPT) closely resembles human preeclampsia. Key pathophysiologic roles for prostacyclin deficiency and/or thromboxane $A_2$ excess have been suggested in preeclampsia. OPT was induced in 5 pregnant ewes (gestational day 135, term 150 days) by 72 hours of starvation. Maternal mean arterial blood pressure (MAP), left uterine arterial blood flow (UBF), platelet count (PC), creatinine clearance (CC), urine protein (UP), and collagen lag phase of in vitro platelet aggregation (CLP) were measured before induction of OPT, during OPT, and following 3 intravenous injections of U-63,557A;sodium5-(3'-pyridinylmethyl)benzofuran-2-carboxylate, monohydrate, (30 mg/kg).

| Time | MAP mmHg | UBF/ml/ min/lamb | CC-ml/ min/kg | UP mg/dl | PC-$10^3$ /mm$^3$ | CLP sec |
|---|---|---|---|---|---|---|
| Pre-OPT | 92±2 | 237±33 | 1.46±.1 | 41±19 | 316±21 | 30±5 |
| OPT | 109±3* | 260±56 | 0.71±.16* | 63±19* | 230±26* | 9.6±5* |
| Post-Rx | 88±5 | 320±54* | 1.09±.23 | 34±17 | 313±38 | 47±21 |

*p<0.03

U,63,557A reduced MAP and concurrently increased UBF. CC was increased, and proteinuria was reduced. Platelet count and CLP were normalized. These data strongly suggest that inhibition of thromboxane synthetase causes resolution of hemodynamic, coagulation, and renal dysfunctions which occur during OPT.

30.14

IN VITRO SECRETION OF ANGIOTROPIC FACTOR BY BOVINE PLACENTA. D.A. Redmer*, D.S. Millaway* and L.P. Reynolds. North Dakota State University, Fargo, ND 58105

Minced explants (193±12 mg) of caruncle (CAR), intercaruncular endometrium (ICAR), cotyledon (COT) and intercotyledonary fetal membrane (ICOT) from 6 cows (≅ day 180 of gestation) were incubated in 10 ml Eagle MEM under 5%$CO_2$, 95% air in a Dubnoff water bath (30 cycles/min, 37°C) for 24 h. Explant conditioned MEM (ECM) was stored at -80°C until assayed. For mitogenesis, bovine aortic endothelial cells (BAEC; 43±1 x $10^3$ cells/well) were incubated in media containing 20% MEM (CONTROL, 3 wells/24-well plate) or 20% ECM (3 wells/tissue) for 72 h and number of BAEC/well determined (Coulter counter). Migration of BAEC through polycarbonate membranes (8 μm pores) was assayed (48-well Boyden chambers) with 58.5 x $10^3$ BAEC in MEM in top wells and MEM (CONTROL, 6-9 wells/chamber) or MEM + 30% ECM (3 wells/tissue) in bottom wells. After 5 h, number of BAEC migrating was determined. For CAR, ECM stimulated mitosis of BAEC greater (P<0.01) than ECM of ICAR, COT, ICOT and CONTROL (113±8 vs. 82±3, 76±2, 82±4 and 86±3 x $10^3$ cells/well). For CAR, ECM also stimulated migration of BAEC greater (P<0.05) than ICAR, ICOT and CONTROL (3.6±0.5 vs. 2.0±0.2, 1.6±0.1 and 2.6±0.2 x $10^3$ cells/well). Number of BAEC migrating was less (P<0.01) for ECM of COT (1.2±0.1 x $10^3$ cells/well) than CONTROL. Thus, the maternal portion of the bovine placenta secretes a factor(s) which stimulates mitosis and migration of vascular endothelial cells.

30.15

A NEW METHOD FOR THE ARTIFICIAL RAISING OF INFANT RATS: THE PALATE CANNULA. Helen H. Blake*, Chantal Lau and Susan J. Henning, Dept. of Biology, Univ. of Houston, Houston, TX 77004

Chronic removal of infant rats from their mother prior to the onset of weaning is complicated by the fact that young rats will not suckle from an artificial nipple. Thus, a method of artificial raising becomes necessary for developmental investigations of nutrition or ingestive behaviors during the suckling period in the absence of maternal variables. The intragastric cannula has been used to study many aspects of the suckling period. However, severe complications limit its use. Furthermore, for many studies it would be advantageous if the diet could be administered to the mouth and actually swallowed by the young rat. We developed a new cannulation procedure which accomplishes these goals. Infant rats were removed from their mother on postnatal day 13 and fitted with a cannula that opened into the oral cavity through the hard palate. Liquid diet was administered by an infusion pump through the cannula for the subsequent 5 days. Growth was assessed by daily measures of body and organ weight. The results indicate that this method of artificial raising of infant rats allows for the continuation of normal growth patterns and eliminates many of the complicating factors associated with other forms of artificial raising. Moreover, ingestion from the palate cannula is voluntary in the sense that the pups are able to reject an unpalatable diet.

30.16

RELATIVE ROLES OF GLUCOCORTICOIDS AND THYROXINE IN POSTNATAL DEVELOPMENT OF INTESTINAL ENZYMES. Susan J. Henning and Tam Le*, Dept. of Biology, Univ. of Houston, Houston, TX 77004.

Previous studies have shown that thyroxine ($T_4$) alone has no effect on jejunal sucrase development, but when $T_4$ is given with cortisol, the precocious increase in sucrase activity substantially exceeds that obtained with cortisol alone. We proposed that this effect is not due to an interaction of $T_4$ with intestinal tissue, but rather to its ability to maintain higher circulating concentrations of cortisol via elevation of corticosteroid-binding globulin (CBG). The 1st expt examined the influence of $T_4$ on serum corticosterone arising from a subcutaneous pellet. As predicted, corticosterone concentrations were much higher in hyperthyroid rat pups than in hypothyroid littermates. The 2nd expt made use of the fact that the synthetic glucocorticoid dexamethasone (DEX) does not bind to CBG. Hypo- and hyperthyroid rat pups received DEX on days 13-15 and were sacrificed on day 16 for assay of jejunal sucrase, maltase and lactase and ileal acid β-galactosidase (ABGase). The predicted results were obtained for sucrase and maltase, i.e., enzyme activities elicited by DEX were the same in hypo- and hyperthyroid animals. However, for lactase and ABGase (2 enzymes which normally decline during development), DEX was without effect in hypothyroid pups but caused precocious maturation in hyperthyroid pups. We conclude that $T_4$ normally plays a permissive role in sucrase and maltase development via elevation of CBG, and an essential role in lactase and ABGase development via synergism with glucocorticoids.

30.17

CORTICOSTERONE KINETICS IN THE DEVELOPING RAT. Lucy L. Leeper* and Susan J. Henning, Dept. of Biology, Univ. of Houston, Houston, TX 77004

To understand the determinants of circulating concentrations of corticosterone in the developing rat, the half-life of disappearance ($T_{\frac{1}{2}}$) and apparent volume of distribution ($V_D$) for a single injection of a tracer dose of $^3$H-corticosterone were determined in rats aged 12, 15-16, and 22 days of age. Metabolic clearance rate (MCR) was calculated, and secretion rate (SR) was derived from MCR and the steady state concentration of hormone under both basal and stress conditions. $T_{\frac{1}{2}}$ and $V_D$ decreased in parallel with increasing age, and consequently MCR displayed no significant change. SR also remained constant with increasing age under basal conditions, but increased significantly with age in stressed rats. Protein binding of the injected $^3$H-corticosterone increased significantly with increasing age. The principal binder, corticosteroid-binding globulin (CBG), increases in concentration with both age and thyroxine ($T_4$) level, so corticosterone kinetics were also examined in hyper- and hypothyroid rats aged 16 days. Protein binding increased with increasing plasma $T_4$ concentrations, and both $T_{\frac{1}{2}}$ and $V_D$ decreased so that MCR was unaffected as in the age studies. SR increased significantly with increasing plasma $T_4$ under both basal and stressed conditions. We concluded that during both normal development and $T_4$ manipulation, protein binding is an important determinant in corticosterone kinetics; however, increased binding is associated with decreased $T_{\frac{1}{2}}$, contrary to common belief.

30.18

MATERNAL-NEONATAL ERYTHROPOIETIC RELATION: POSSIBLE TRANSFER OF ERYTHROPOIETIN VIA MATERNAL MILK. R.D. Carmichael, J. LoBue* and A.S. Gordon. Morgan State Univ., Baltimore, Md. 21239, New York Univ., N.Y. 10003

Erythropoiesis was stimulated in neonatal rats nursed by phlebotomized mothers. This was judged by increases in hematocrit, hemoglobin, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Failure to observe increases in reticulocytes may be, in part, the result of decreased maturation time, as indicated by reticulocyte Heilmeyer maturation indicies in peripheral blood. Quantitative studies of the spleen revealed a significant decrease in total numbers of nucleated RBC/mg spleen in 11-day-old neonates suckled by the anemic mother which returned to control values by day 12. A significant decrease in total numbers of nucleated RBC/mg marrow was seen in both 11 and 12-day-old neonates of anemic mothers when compared to control values. These results suggest that: 1) Erythropoietin (Ep) is transmitted to nursing rats via maternal milk, and by escaping inactivation, at least to some extent, in their gastrointestinal tract stimulates their erythropoiesis; 2) Ep exerts its influence predominantly at the level of the differentiated erythroid cell compartment probably by causing a shortening of the mean transit time of the proliferating erythroblast compartment and/or a decrease in the maturation time of the nonproliferating orthochromatic and reticulocyte compartment. This work was supported by a grant from NIH #HL03357.

## TUESDAY PM CORONARY PHYSIOLOGY

33.1

XANTHINE OXIDASE INHIBITION FAILS TO LIMIT INFARCT SIZE IN THE RABBIT. James Downey, David Chambers*, Tetsuji Miura*, Derek Yellon*, Dale Jones*. Univ. South Alabama, Mobile, AL 36688 and St Thomas' Hospital, London, UK.

We have proposed that xanthine oxidase (XO) is a source of free radicals in dog heart since inhibition of XO with allopurinol limited infarct size following coronary occlusion. The rabbit heart, like the human heart, has undetectable levels of XO. We, therefore, examined superoxide dismutase (SOD), 165 U/min/Kg IV for 90 min; catalase (CAT), 555 U/min/Kg IV for 90 min; CAT + SOD; or allopurinol, 75 mg PO 24 hrs before surgery then 30 mg/kg IV 15 min before occlusion; in an ischemia-reperfusion model in rabbit. We occluded a coronary branch of an open-chest anesthetized rabbit for 45 min. After 3 hrs of reperfusion we removed the heart, reoccluded, and irrigated with 1-10 u fluorescent particles in saline to mark the risk region. The heart was sectioned and necrosis was visualized by tetrazolium stain. 67+-4% of the risk zone infarcted in the 12 control hearts, SOD+CAT limited this to 35+-3% (n=10, p<.01). % infarction was not different from control with either allopurinol (65+-3%, n=9), SOD (59+-9%, n=7), or CAT (74+-4%, n=6). Ischemia-reperfusion injury in the rabbit was free radical related as evidenced by the protection afforded by SOD + CAT. XO inhibitors may not be protective in the coronary patient since the human heart contains little or no XO.

33.2

CORONARY VASODILATION DURING GLOBAL MYOCARDIAL HYPOXIA IS ABOLISHED BY ADENOSINE DEAMINASE. Gary F. Merrill, Hwu M. Wei* and Young H. Kang*. Program in Physiology, Rutgers University, New Brunswick, NJ 08903.

We have recently reported that adenosine deaminase (ADA) attenuates the coronary vasodilation of systemic (AJP 250:H567, 1986) and regional myocardial (Fed. Proc. 45:396, 1986) hypoxia. These studies were conducted in anesthetized, instrumented dogs. To avoid intervening, neurohumoral complications we used the isolated, Krebs-Ringer perfused guinea pig heart (n=21) to investigate the effects of ADA on the coronary vasodilation of mild global myocardial hypoxia. Results are presented in the following table:

| | Before ADA | | After ADA | |
|---|---|---|---|---|
| | Control | Hypoxia | Control | Hypoxia |
| CF (ml/min/g) | 6.6±0.2 | 10.3±0.3 | 6.0±0.3 | 6.1±0.3* |
| $MVO_2$ (ul/min/g) | 38.4±1.2 | 35.5±2.4 | 38.3±1.4 | 23.9±1.9* |
| $(a-\bar{v})O_2$ (ul/ml) | 5.9±0.3 | 3.5±0.2 | 6.5±0.3 | 4.0±0.3* |

*P<0.05 relative to hypoxia before ADA.

Heart rate was spontaneous and remained constant throughout. Peak left ventricular systolic pressure and its $dP/dt_{max}$ decreased significantly during hypoxia. The greatest decrement was seen after ADA administration. Under moderate conditions of hypoxia (CF increased 2-fold, data not shown) ADA attenuated the vasodilation by >85%. We conclude that adenosine is responsible for the coronary vasodilation of mild to moderate global myocardial hypoxia in the isolated guinea pig heart.

33.3

MAINTENANCE OF VASCULAR TONE IN ISOLATED BOVINE CORONARY ARTERY BY ADENOSINE. M. V. Ramagopal* and S. Jamal Mustafa, Department of Pharmacology, School of Medicine, East Carolina University, Greenville, NC, 27834.

Adenosine (Ad) dilates the coronary artery (CA), when pre-contracted with various constrictor agents. There is not enough information regarding the effects of adenosine on unstimulated CA. The present study was an attempt to determine the mechanism for the action of Ad in the maintenance of CA tone. Bovine CA rings (LAD branches; 2+.1 o.d.; 2-3 mm wide) were used to study the effect of Ad on basal tone, $Ca^{2+}$-influx and $Ca^{2+}$-efflux during unstimulated conditions. Relaxing effect of Ad in CA was measured using muscle baths. For $Ca^{2+}$-influx studies, after 3 hrs incubation in normal PSS at 37°C, the rings were loaded with $^{45}Ca^{2+}$ in the presence of Ad for 10 min. The rings were further incubated in $Ca^{2+}$-free+2 mM EGTA PSS for 30 min. at 0°C. $Ca^{2+}$-efflux was measured in $Ca^{2+}$-free medium after loading the tissues for 2 hrs with $^{45}Ca^{2+}$. Ad produced concentration-dependent relaxations, which were reversed completely by Ad deaminase. Ad and its analogs (NECA and L-PIA) produced dose-dependent inhibition of $Ca^{2+}$-influx. 8-Phenyltheophylline reversed the inhibitory effects of Ad and its analogs on $Ca^{2+}$-influx. Ad ($10^{-5}$-$10^{-4}$ M) increased $Ca^{2+}$-efflux in unstimulated arteries. These data suggest that Ad in vitro relaxes the CA in part due to inhibition of $Ca^{2+}$-influx and in part due to $Ca^{2+}$ extrusion under unstimulated conditions. (Supported by HL 27339)

33.4

THE SIGNIFICANCE OF ENDOTHELIAL FUNCTION IN MAINTENANCE OF FLOW THROUGH STENOTIC ARTERIES. T. Kikuchi*, B. Sigel*, W. Santamore & T. Tulenko. The Medical College of Penna., Phila., Pa.

The object of this study was to evaluate the role of endothelial function in flow regulation in stenosed arteries. Canine carotid arteries were perfused in-vitro at 40 ml/min under 100 mmHg pressure with PSS. Proximal and distal pressure and flow were monitored while luminal dimensions were measured using m-mode ultrasonography. A silicone plug shaved along its longitudinal axis to remove 15% cross sectional area was fixed into the lumen creating a compliant stenosis and pressure drop of 8-10 mmHg. Dose response analyses to serotonin (5-HT) delivered luminally were performed +/- endothelial denudation and also in endothelial intact segments +/- 10 uM oxyhemoglobin (Hbg). In the presence of endothelium, 5-HT produced dose-dependent reductions in flow culminating in complete occlusion. Following denudation, the sensitivity to 5-HT increased 10 fold. In endothelial intact segments, luminal Hgb also increased 5-HT sensitivity 10-fold and adventitial Hgb increased it 5-fold. Following denudation, Hbg failed to alter 5-HT sensitivity. Using ring segments of the same vessels isolated for isometric analysis, the Hbg effect on endothelial-mediated relaxations was abolished in the presence of 10uM methylene blue. We conclude from these studies that normal endothelial function contributes to the maintenance of flow in critically stenosed arterial segments, and that endothelial damage or its inactivation by local Hgb amplifies the vasoconstrictor action of serotonin with the potential for precipitating vasospastic episodes in large arteries. (Supported by NIH Grants HL30496 & AG04908)

33.5

EFFECT OF DOBUTAMINE ON DISTRIBUTION OF MYOCARDIAL BLOOD FLOW IN A RESTRICTIVE CORONARY BED. M.A. Kapin, B. Myer*, C. Stefanu*, F.A. Bashour. The University of Texas Health Science Center at Dallas. 75235.

Ability of Dobutamine (Db) to influence distribution of myocardial blood flow (MBF) was investigated in 12 dogs (6 received saline (NSS), and 6 Db). The left anterior descending artery (LAD) was perfused with constant-blood flow (38+2 ml/min). MBF was measured using 15+1 $\mu$ microsphere during 4 periods: $P_1$ before, $P_2$ and $P_3$ after 10 min of 5 and 10 $\gamma$ Db or NSS respectively, and $P_4$ after cessation of the drug. NSS failed to effect cardiac output (CO) or coronary perfusion pressure (CPP) while Db increased CO from 2548+294 ml/min in $P_1$, by 32% and 37% in $P_2$ and $P_3$, respectively. Db statistically decreased CPP from $P_1$ (120+8 mmHg) by 13% and 23% in $P_2$ and $P_3$ respectively, and back to control in $P_4$ (Paired T-statistic, $p<.05$). MBF was decreased during NSS (17% and 7% during $P_2$ and $P_3$). Db uniformly increased MBF above control in all regions of the heart by 23% and 14% at $P_2$ and $P_3$, respectively (Sign test, $p<.05$). There was no change in the epicardial/endocardial ratio during both NSS and Db treatments. Since LAD flow was kept constant, the increase in flow to regions supplied by LAD, must have come from adjacent vessels. (Supported by Cardiology Fund).

33.6

CHARACTERIZATION OF THE SOMATIC COMPONENT TO EXPERIMENTALLY INDUCED MYOCARDIAL INFARCTION: MUSCLE. D.A. DeBias, C.H.Greene, D.Heilig*, A.S.Nicholas*, W.V. Harrer*, Philadelphia College of Osteopathic Medicine, Philadelphia, PA 19131.

It is a fundamental tenet of osteopathic medicine that visceral and somatic components may manifest at sites remote from the disease focus, and these sites may be segmentally related. As such, these components may be considered as integral parts of the pathophysiology. A somatic component has been demonstrated to be associated with acute myocardial infarction and consists of paravertebral soft tissue changes detectable by palpation (1). The study reported here was designed to characterize and quantify the somatic component in a canine model in which non-fatal myocardial infarction was induced by coronary artery occlusion. Muscle, fascia, fat, and skin biopsied from the involved area are under analysis using morphometric techniques and electrophotomicroscopy. The changes in the paravertebral somatic component have been documented and indicate a reorganization of the contractile state of the skeletal muscle; altered metabolic activity at the site is also apparent.

(Supported in part by the AOA Bureau of Research and in part by Phila.College of Osteopathic Medicine.

(1) Nicholas, et al., BMJ. 291: 13-17, 1985.

33.7

OVERLAP OF CORONARY PERFUSION TERRITORIES IN NORMAL AND COLLATERALIZED CANINE HEARTS. H. Fred Downey, Noriyasu Watanabe*, Shuji Yonekura*, and Arthur G. Williams*. Tex. Coll. Osteopath. Med., Ft. Worth, TX 76107

The "shadow technique" (Circ. Res. 39:214, 1976) is frequently utilized to identify tissue sections free of "contamination" from overlapping, adjacent perfusion fields. The basic assumption of the shadow technique is absence of collateral flow between coronary arteries perfused at similar pressures. Implicit is the assumption that all coronary collateral channels originate and terminate at equal pressures. This investigation examined the extent of overlap-free tissue in normal (NM, n=3) and collateralized myocardium (CM, n=3). We also determined if peripheral coronary embolization would alter the amount of overlap-free tissue in CM. Perfusion territories were delineated by intracoronary injection of India ink, and regional flow was measured by tracer microspheres in tissue sections averaging 0.46+0.01 g. For perfusion territories of 29.3+3.5 g in CM and 35.5+4.8 g in NM, overlap-free tissue averaged 8.3+4.4 g and 26.9+3.9 g, respectively. When collateral flow was limited by peripheral embolization, the overlap-free region increased by 173% to 14.4+6.1 g. Thus, collateral flow causes the shadow technique to overestimate perfusion territory overlap, especially in CM. (Supported by HL-35027.)

33.8

ROLE OF CORONARY DISTENDING PRESSURE IN DELAYED MYOCARDIAL ISCHEMIA. Panos Papageorgiou*, Richard L. Verrier, Eric L. Hagestad* Dept. of Physiology, Harvard Medical School, and Cardiovascular Labs., Harvard School of Public Health.

In the presence of critical coronary stenosis, cessation of left stellate ganglion stimulation (LSGS) results in delayed myocardial ischemia (DMI). This occurs when blood pressure (BP) returns to normal. Based on this observation and our previous finding that prazosin blocks the DMI response, it was pertinent to determine whether myocardial ischemia could be evoked by preventing the hypertensive response during LSGS. Seven morphine-chloralose anesthetized dogs were instrumented to record BP, left circumflex arterial pressure (CP) and flow (CBF). Control values were obtained after a critical coronary stenosis was produced using an adjustable occluder. LSGS alone or with BP control by means of exsanguination yielded the following results (means+SEM, *$p < 0.03$):

| | mean BP(mmHg) | mean CP(mmHg) | CBF(ml/min) |
|---|---|---|---|
| Control | 95+5 | 69+8 | 16+2 |
| LSGS | 131+8* | 75+9 | 22+2* |
| +Exsanguination | 98+7 | 35+6* | 7+2* |
| +Reinfusion | 125+14* | 58+12 | 18+5 |

Thus, when the pressure increase produced by LSGS is prevented, myocardial ischemia occurs during sympathetic activation. We conclude that the temporal properties of the DMI phenomenon result from an interaction between coronary distending pressure and adrenergic constrictor tone.

33.9

DEVELOPMENT OF AN INTRACORONARY PRESSURE GRADIENT DURING DELAYED MYOCARDIAL ISCHEMIA. Eric L. Hagestad*, Panos Papageorgiou*, and Richard L. Verrier. Cardiovascular Labs, Harvard School of Public Health, and Department of Physiology, Harvard Medical School, Boston MA 02115.

With critical coronary stenosis, rapid cessation of left stellate ganglion stimulation (LSGS) can result in delayed myocardia ischemia (DMI). To determine the precise location of the presumed vasoconstriction, experiments were carried out in eleven chloralose anesthetized dogs with critical stenosis of the left circumflex coronary artery. The animals were instrumented for recording aortic blood pressure (BP). Flow (CBF) and pressure (CBP) distal to the site of stenosis were also monitored. The specific resistance in the left circumflex coronary artery (CxR) was defined as the pressure gradient (BP - CBP) divided by the CBF. Results obtained during the 30 seconds of LSGS, and 90 seconds following its abrupt cessation are expressed as means ± SEM (*p< 0.001).

| | BP(mmHg) | CBF(ml/min) | CP(mmHg) | CxR(mmHg/ml/min) |
|---|---|---|---|---|
| control | 94±4 | 14±2 | 74±4 | 2±0 |
| LSGS | 139±8* | 20±3* | 72±10 | 4±1* |
| post-LSGS | 95±6 | 4±0* | 34±6* | 22±4* |

Delayed ischemia is thus associated with a substantial increase in the resistance within the stenosed coronary artery. Based on this finding and our previous observation that alpha-adrenergic blockade prevents the DMI response, we conclude that this phenomenon is due primarily to active constriction of the circumflex coronary artery.

## NEURAL CONTROL OF CIRCULATION II

34.1

SUMMATION OF VAGAL NERVE FIBERS OF THE CANINE HEART. Sally A. Lang* and Matthew N. Levy. The Mt. Sinai Medical Center, Cleveland, OH 44106

We examined the additive effects of right and left vagus nerve stimulation on atrial contractility by comparing the responses of combined vagal stimulation to the sum of the responses to individual right and left vagal nerve stimulation in pentobarbital-anesthetized dogs. The values are means ± SE; n = 4.

| STIMULATION LEVEL | PERCENT INHIBITION OF ATRIAL CONTRACTILITY Combined | Sum | Signif |
|---|---|---|---|
| LOW | 30.8 ± 2.2% | 27.2 ± 1.5% | NS |
| MEDIUM | 49.4 ± 3.7% | 50.2 ± 2.4% | NS |
| HIGH | 64.4 ± 2.8% | 81.6 ± 2.3% | <0.05 |

At the low and medium stimulation levels, the negative inotropic response calculated as the algebraic sum of the individual responses to right and left vagal nerve stimulation was not significantly different from that produced by combined vagal nerve stimulation. In contrast, at high stimulation strengths, the sum of the responses to individual nerve stimulation was significantly greater than that resulting from combined vagal stimulation. The nonlinear summation observed at higher stimulation levels may represent occlusion at the synapses between the pre- and postganglionic vagal fibers, or saturation of the receptors at the level of the cardiac effector cells.

34.2

DEVELOPMENT OF BLOOD PRESSURE SUPPORT MECHANISMS AFTER NEONATAL SYMPATHECTOMY. E. Mills, J.W. Bruckert & P.G. Smith. Dept. Pharmacology. Duke Med. Ctr. Durham, N.C. 27710.

Rats were treated with guanethidine (SNX) from birth through 50 days. In in vivo experiments at 18, 25, 40, 60, 70 and 100 days we measured maximum and ED50 of pressor response to the α-1 noradrenergic agonist methoxamine and sequential hypotensive responses to adrenalectomy, ganglionic blockade (chlorisondamine),α1,2 noradrenergic blockade (phentolamine), antagonists of ANG II and AVP and direct acting vasodilator (hydralazine). In SNX rats there was no pressor response to tyramine evoked release of endogenous NE, decreased Plasma NE (70%) with EPI unchanged and supersensitivity (decreased methoxamine ED50). SNX did not affect development of the maximum of the methoxamine pressor response. Resting MAP was 7 - 20% lower in SNX rats. MAP after ganglionic blockade was 27 - 36% higher in SNX. SNX eliminated hypotensive responses to chlorisondamine and decreased responses to phentolamine. In contrast, SNX increased responses to ANG II antagonist (70 - 240%); AVP antagonist (250%) and hydralazine (50 - 300%). MAP at maximum dilation with hydralazine was not affected in SNX. We conclude that after SNX at birth (1) vascular noradrenergic contractility and intrinsic resistance develop normally (2) MAP is independent of circulating catecholamines despite supersensitivity (3) MAP is supported by enhanced pressor influence of vasoactive substances including ANG II and AVP. (Supported by NIH grant HL 29403 and AHA E.I. 83-118)

34.3

HINDLIMB BLOOD FLOW DURING MODERATELY HIGH INTENSITY RUNNING IN RATS WITH AND WITHOUT INTACT SYMPATHETIC INNERVATION. D. Fred Peterson, K.R. Rouk*, and E.A. Lowenthal*, Oral Roberts University Medical School, Tulsa, OK 74171.

The involvement of sympathetic innervation in blood flow regulation was studied in 32 hindlimb muscles and 13 other selected tissues using the radiolabeled microsphere technique. Catheters were placed in the ascending aorta and renal artery for microsphere injection and blood sampling. The $L_2$-$L_4$ region of the sympathetic chains were looped in one group of rats 48 hours prior to experimentation to enable acute denervation. Control (C) and acutely sympathectomized rats (S), were compared prior to exercise and at 0.5, 2 and 5 min of treadmill running at 45 m/min. Total hindlimb muscle blood flow is found in the table. Values are mean ± SEM in ml/min/100 gm tissue. Number of animals is in parentheses.

| | Pre-Ex | 0.5 min | 2 min | 5 min |
|---|---|---|---|---|
| C | 45±3(8) | 112±15(8) | 136±8(8) | 125±8(12) |
| S | 50±6(11) | 107±14(11) | 131±12(9) | 128±16(9) |

All values during exercise were greater than preexercise. There was no difference between C and S at any point in time. In contrast, a previous report showed that low intensity exercise (15 m/min) elevated hindlimb blood flow in acutely sympathectomized rats at 5 min of running (Fed Proc 43:699, 1984). The present results indicate that at moderately high levels of exercise the sympathetic nervous system does not restrain blood flow to exercising muscles as it does during less intense exercise. Supported by AHA 831047.

34.4

ACTIVATION OF THE PULMONARY CHEMOREFLEX EVOKES REFLEX DILATION OF SMALL ARTERIOLES IN RAT SKELETAL MUSCLE. A.M. Roberts and I.G. Joshua. Dept. of Physiology and Biophysics, Health Sciences Ctr., Univ. of Louisville, Louisville, KY 40292.

Activation of vagal afferent fibers in the lungs evokes reflex changes in heart rate and blood pressure. We have attempted to determine if activation of pulmonary C-fibers affects the tone of small resistance vessels in skeletal muscle. In pentobarbital-anesthetized male Sprague-Dawley rats (n=5), we examined the in vivo responses of small arterioles (19.6 ± 4.3μm) in the cremaster muscle, using closed circuit television microscopy. Stimulation of pulmonary C-fibers by injecting capsaicin (5μg/kg) into the right atrium, caused a rapid dilation (64 ± 15%) of small arterioles, and decreased blood pressure and heart rate (pulmonary chemoreflex). Effects were abolished by sectioning the cervical vagus nerves. Arteriolar responses did not appear to be secondary to hemodynamic changes, since similar decreases in blood pressure to the rat hindlimbs (produced by partial occlusion of the abdominal aorta), caused constriction of small arterioles. Thus, it appears that reflex dilation of small arterioles in skeletal muscle contributes to the fall in blood pressure associated with stimulation of pulmonary C-fibers. (Supported in part by a grant from the American Heart Association).

34.5

EFFECT OF RAPID EYE MOVEMENT (REM) SLEEP PERIOD TERMINATION ON BLOOD PRESSURE AND HEART RATE. S. DeMesquita* and G.V. Guyer* (SPON: K.E. Guyer). Marshall Univ., Huntington, WV 25704-2901.

Hypotensive episodes have been noted to occur following the termination of REM sleep in rats (Junqueira and Kreiger, J. Physiol. 259:725, 1976). Ten male normotensive Sprague-Dawley rats were each instrumented with a chronic aortic cannula, EEG and EMG electrodes in order to monitor blood pressure and heart rate during all sleep state transitions. A mean of the peak systolic blood pressure and heart rate for the ten seconds before and after the point of each transition was obtained for a total of 374 transitions.

There was no significant change in peak systolic blood pressure or heart rate at the transitions from Wake to Non-REM sleep, Non-REM to REM or Non-REM to Wake. The transition from REM to Non-REM, regardless of the level or duration of arousal at the point of transition, was found to have a significant ($P<0.01$) decrease in peak systolic blood pressure [130 ± 2 mmHg (mean ± SE) in REM to 122 ± 2 mmHg in Non-REM] and a significant ($P<0.01$) increase in heart rate (324 ± 7 beats/min in REM to 351 ± 6 beats/min in Non-REM). The transition from REM to Wake also had a significant ($P<0.01$) decrease in peak systolic blood pressure (128 ± 3 mmHg in REM to 116 ± 4 mmHg in Wake) and a significant ($P<0.01$) increase in heart rate (321 ± 8 beats/min in REM to 345 ± 8 beats/min in Wake).

Thus the termination of REM sleep, but not Non-REM sleep or Wake, was associated with a brief but significant period of hypotension and tachycardia in the adult rat.

34.6

A MATHEMATICAL MODEL OF CAROTID SINUS BARORECEPTORS. J.F.M. van Brederode*, J.L. Seagard, F.A. Hopp*, and J.P. Kampine. Depts. of Anesthesiology and Physiology, Medical College of Wisconsin and VA Medical Center, Milwaukee, WI 53295

Most mathematical models used to describe the relation between carotid sinus pressure (CSP) and carotid sinus nerve firing frequency (f) have not taken into account the electrical properties of the baroreceptor membrane and spike-initiation zone (SIZ). The purpose of this study was to develop and validate a model of the baroreceptors which could be used to evaluate our experimental observations on the effects of variations in extracellular sodium concentration ($Na_e$) on single A- and C-fiber discharge frequency ($f_A$ and $f_C$) in an isolated carotid sinus preparation in the dog when subjected to ramp changes in CSP. The model describes the relation between CSP, sinus wall strain and receptor deformation and assumes that the electrical properties of the receptor are determined by the Nernst equilibrium potentials for sodium and potassium ($E_{Na}$ and $E_K$) weighted for their ionic conductances ($g_{Na}$ and $g_K$) electrotonically coupled to the SIZ with f proportional to the receptor membrane potential ($E_r$). Comparison of experimental and calculated values for the exponential CSP-$f_A$ relation indicated that variations in Na affect maximum $f_A$ and that this effect is only partly due to changes in $E_r$ through actions of $Na_e$ on $F_{Na}$. In addition to changing $E_r$, a change in $Na_e$ caused a change in threshold at the SIZ resulting in a parallel shift of the S-shaped CSP-$f_C$ relation. Supported by VA 7759-02P.

34.7

RABBIT CAROTID BARORECEPTER ACTIVITY AND SINUS DIMENSIONS BEFORE AND AFTER INTRASINUS PROTEASE TREATMENT. H.O. Stinnett and M.D. Olson*. Depts. Physiol. & Anat. UNDSM, Grand Forks, ND 58202.

Following vascular isolation and sinus efferent denervation baroreceptor nerve activity (BNA) and outside dimensions (DIM) were recorded during change in non pulsed intrasinus pressure (ISP) before and after limited intrasinus exposure to Protease (0.1 mg/100ml Ringers, 15 min, 37° C). Prior to enzyme treatment, the relationship of BNA to ISP showed clockwise hysteresis when ISP was increased stepwise (15 mmHg, 1 min) from 25 to 100 to 25 mmHg. Concurrently, the relationship of DIM to ISP showed counterclockwise hysteresis. Protease altered the relationship slope of DIM to ISP and abolished the hysteresis. Prior to enzyme treatment, when ISP was increased in one step from 25 to 70 mmHg and held constant for 20 min BNA decreased and DIM increased in non linear manner, respectively. Following Protease use both of these responses were altered with an overall increase in DIM and decrease in BNA. Comparison of TEM sections showed sinuses exposed to Protease had extensive loss of endothelium and damage of adluminal layers of tunica media smooth muscle membranes, however no detectable effect was found at or beyond the media-adventitia border. Results indicate an important influence of tunica media viscoelastic elements on the relationship of multifiber BNA to ISP. Supported in part by BRSG S07 RR05 407-22, Div. Research Resources NIH and Heart Research 5804 (2902).

## RENAL-CARDIOVASCULAR INTEGRATION

35.1

ROLE OF ATRIAL NATRIURETIC FACTOR (ANF) IN MEDIATING THE NATRIURESIS INDUCED BY ACUTE VOLUME EXPANSION. Ali A. Khraibi, Kevin R. Walker*, John C. Burnett, Jr., and Joey P. Granger, Department of Physiology, Mayo Clinic and Foundation, Rochester, MN 55905

The purpose of this study was to determine the role of ANF in mediating the natriuresis induced by acute volume expansion. Glomerular filtration rate (GFR), fractional sodium excretion ($FE_{Na}$), and plasma levels of ANF ($P_{ANF}$) were determined in control rats and rats undergoing acute volume expansion (5% of b.w. in 30 min). In a third group, synthetic ANF (8-33) was infused at a dose to mimic circulating levels of ANF achieved during acute volume expansion. $P_{ANF}$ was determined by radioimmunoassay from extracted arterial plasma.

| | $P_{ANF}$ (pg/ml) | GFR (nl/min) | $FE_{Na}$ (%) |
|---|---|---|---|
| Control (n=4) | 123±25 | 2.64±0.39 | 0.85±0.14 |
| Volume Expansion (n=8) | 368±22* | 3.52±0.18* | 6.56±1.01* |
| ANF-infused (n=13) | 389±36* | 3.00±0.11 | 3.15±0.24* |

*p<0.05 vs control

In summary, acute volume expansion produced a significant increase in $P_{ANF}$, GFR, and $FE_{Na}$ as compared with control. Infusion of ANF at a dose to mimic $P_{ANF}$ obtained during volume expansion resulted in a threefold increase in $FE_{Na}$ without a significant increase in GFR. We conclude that ANF may be important in promoting natriuresis during acute volume expansion by decreasing tubular reabsorption of sodium. (Supported by NIH Grants # AM07013 and HL33947).

35.2

ROLE OF ANGIOTENSIN II SUPPRESSION AND PROSTAGLANDIN IN ANP-INDUCED NATRIURESIS. F. J. Salazar*, M. D. Bentley*, J. P. Granger, M. Fiksen-Olsen* M. Joyce*, and J. C. Romero. Mayo Clinic, Rochester, MN, 55905.

We have previously shown that the natriuresis induced by the infusion of ANP, at a dose that does not alter renal hemodynamics and blood pressure (BP), is associated with a decrease in renin secretion and an increase in prostaglandin (PG) excretion. The present study was undertaken to examine the influence of both angiotensin II (AII) and PG on natriuresis induced by ANP. The intrarenal (i.r.) infusion of ANP (0.05 µg/kg/min; n=6) produced significant increases ($p<0.05$) in fractional excretion of sodium (FeNa) and lithium (FeLi). When a simultaneous i.r. infusion of converting enzyme inhibitor (1 µg/kg/min) and AII (1.2 ng/kg/min) were given to maintain constant intrarenal levels of AII, the natriuresis induced by ANP infusion was inhibited by 39% ($p<0.05$) and the increment in FeLi was prevented. Renal hemodynamics and BP did not change throughout the study. In a second experimental group (n=6), the administration of meclofenamate (5 mg/kg, i.v., n=3) or indomethacin (10 µg/kg/min, i.r., n=3) prevented the ANP-induced redistribution of RBF to the deep cortex as estimated by microspheres. However, the increments of FeNa and FeLi ($p<0.05$) were similar to that induced by the administration of ANP alone. These results suggest that the natriuretic effect of ANP is partly mediated by the intrarenal suppression of AII and that PG are unrelated.

35.3

ROLE OF LEUKOTRIENES IN RENAL WATER EXCRETION. Dale Hartupee and John Passmore. University of Louisville, School of Medicine, Louisville, KY 40292.

We investigated the contribution of leukotrienes (LT) to the control of urine osmolality and urine flow rate. In 8 anesthetized dogs, arachidonic acid (AA, 30 µg/kg•min) was infused intrarenally during blockade of prostaglandin (PG) synthesis with ibuprofen (12.5 mg/kg) to stimulate renal LT synthesis. Although there was no change in renal blood flow (RBF) (1.77±0.20 ml/min•gm before and 1.90±0.45 after), urine osmolality decreased from 893±146 mOsm/kg to 600±122 ($p<0.05$) and urine flow rate concomitantly increased from 0.37±0.12 to 0.60±0.18 ml/min ($p<0.05$). To test whether these effects were due to stimulated LTs, we studied 6 dogs with simultaneous blockade of both PG and LT synthesis with ibuprofen (12.5 mg/kg) and propylgallate (1 mg/kg•hr), respectively. In these animals, intrarenal AA infusion did not alter RBF, urine osmolality (1141±153 mOsm/kg before to 1114±113 after) nor urine flow rate (0.25±0.03 ml/min before to 0.26±0.03 after). Similar results were found in preliminary studies (n=2) using the LT antagonist LY 171883, [2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5yl) butoxy] phenyl] ethanone, instead of propylgallate. Ruling out a non-specific fatty acid effect, intrarenally infused oleic acid (30 µg/kg• in) had no effect on RBF, urine osmolality or flow rate (n=6). We conclude that leukotrienes may decrease urine osmolality, increase urine flow rate and play a role in the control of renal water excretion. (Supported by AHA, Kentucky Affiliate)

35.4

THE EFFECT OF VAGOTOMY ON THE RENAL RESPONSE TO VOLUME EXPANSION IN ATRIAL APPENDECTOMIZED DOGS. B.A. Benjamin*,N.L. Hurst, J.A Richardson* and T.V. Peterson. Dept. of Med. Physiology, Texas A&M Univ. Coll. of Med., College Station, TX 77843

Previously we showed that the renal response to volume expansion (VE) in the dog was not altered by atrial appendectomy. The purpose of the present study was to determine if increased vagal afferent activity compensated for the loss of the atrial appendages. Experiments were carried out in 5 sham (S) and 6 atrial appendectomized (A) animals 4-6 wks after chronic surgery. Each animal was anesthetized and the cervical vagi ligated. 90 min post-vagotomy, a 30 min control period was followed by a 20% isochemic VE and 120 mins of post-VE measurements. Results showed that vagotomy increased control urine flow and sodium excretion. After VE salt and water excretion increased transiently, in both S and A, compared to nonvagotomized animals. The increase in urine flow and sodium excretion after VE were similar in S and A post-vagotomy. Urine flow increased from 1.55±0.25 ml/min to a peak of 2.07±0.29 in S and from 1.08±0.24 to 1.85±0.25 in A. Sodium excretion increased from 279±58 uEq/min to a max of 329±69 in S and from 217±43 to 359±49 in A. Fractional sodium excretion and mean arterial and central venous pressures increased similarly in both groups. Since the renal response to VE was not altered by atrial appendectomy in the intact or vagotomy animals, this suggests that vagal afferents do not compensate for the loss of the atrial appendages. (Supported by NIH Grants HL31987 and HL01383 and Texas Heart Grant 85G-027).

35.5

CARDIOVASCULAR ROLE OF VASOPRESSIN DURING ACUTE HYPERCAPNIA IN THE CONSCIOUS RAT. B.R. Walker, Tulane University School of Medicine, New Orleans, LA 70112.

Experiments were performed to test for the possible involvement of arginine vasopressin (AVP) in the systemic cardiovascular response to acute hypercapnic acidosis in conscious, chronically instrumented rats. Exposure to 6% $CO_2$ caused arterial $PCO_2$ to rise from 34±2 to 53±1 torr (n=6). This level of hypercapnia was associated with a consistent bradycardia, however cardiac output, blood pressure and total peripheral resistance were not significantly affected. Administration of 10 ug/kg i.v. of the specific $V_1$-vasopressinergic antagonist $d(CH_2)_5Tyr(Me)AVP$ (n=6) during 6% $CO_2$ had no effect on any of the measured hemodynamic variables. Furthermore, the antagonist had no effect in normocapnic control animals (n=6). Exposure to a more severe level of hypercapnia (10% $CO_2$; $PaCO_2$ = 89±1 torr) (n=6) resulted in marked hemodynamic alterations. Profound bradycardia and decreased cardiac output in addition to increases in mean arterial blood pressure and total peripheral resistance were observed. $V_1$-vasopressinergic antagonism (n=6) during 10% $CO_2$ had no effect on heart rate, but greatly increased cardiac output. In addition, blood pressure fell and resistance was decreased below pre-hypercapnic levels. The increase in cardiac output was totally attributable to an increase in stroke volume. These data suggest that a number of the hemodynamic alterations associated with severe hypercapnic acidosis in the conscious rat may be mediated by the peripheral vasoconstrictor effects of enhanced AVP release.

35.6

DIFFERENT CARDIOVASCULAR RESPONSES TO $V_1$-VASOPRESSINERGIC ANTAGONISM IN CONSCIOUS VS. ANESTHETIZED RATS. B.L. Brizzee* and B.R. Walker, Tulane University School of Medicine, New Orleans, LA 70112.

Circulating levels of arginine vasopressin (AVP) are increased in animals exposed to anesthesia and surgical stress. Experiments were performed to compare the vasoconstrictor influence of AVP in anesthetized, surgically stressed rats with that in conscious rats. One week prior to study, rats were instrumented with a pulsed Doppler flow probe on the left renal artery and with femoral catheters. Rats were studied under the following conditions: 1) conscious and unrestrained, 2) minor surgery (ketamine - 110 mg/kg plus skin incision), 3) major surgery (ketamine plus laparatomy). After control measurements of blood pressure (MABP) and renal blood flow (RBF), a specific $V_1$-vasopressinergic antagonist ($d(CH_2)_5Tyr(Me)AVP$ - 10 ug/kg, i.v.) was administered. Five minutes after administration of antagonist there were no changes in MABP and RBF in conscious rats. In contrast, in the minor surgery group MABP decreased 14% from control while RBF decreased 11%. The reductions in MABP and RBF were greater in the major surgery group, 29% and 27%, respectively. These data indicate that increased circulating levels of AVP during anesthesia and surgical stress contribute to maintenance of MABP and RBF.

35.7

CENTRAL ATRIAL NATRIURETIC FACTOR INHIBITS DEHYDRATION- AND HYPOVOLEMIC-INDUCED THIRST. M.L. Leavitt, E.J. Riley* and K. Simpson*. Allegheny-Singer Research Inst., Pittsburgh, PA 15212 and Southwest Missouri State Univ., Springfield, MO 65804.

The effects of lateral intracerebroventricular (ivt) administration of rat atrial natriuretic factor (ANF, 8-33) on both dehydration and hypovolemic-induced thirst were tested in male Wistar rats. In the dehydration study rats were water deprived for 18-19 hr followed by infusion of either 2 µl of artificial CSF (veh) alone or containing ANF (0.2 nmoles). Significant inhibition of water intake occurred in ANF-treated rats at each measurement time over a 2 hr period. In other studies, hypovolemia was induced by sc injection of 30% polyethylene glycol after which food, water and 1.8% NaCl were removed for 24 hrs. Veh (10 µl) or ANF (2.0 nmoles) were then infused ivt and cumulative water and salt intakes were monitored every 0.5 hr over the next 4 hr. ANF-treated rats consistently drank significantly less water than controls after 90 min. These rats also consistently consumed less salt than controls after 30 min. with statistical significance reached at 150 and 210 min. Intakes at 210 min.were 28.9±2.5 ml (±SEM) water for veh vs 22.1 ±1.5 for ANF ($p<.05$) and 15.8±2.3 ml salt for veh vs 10.5±1.8 for ANF ($p<.05$). Intake of salt relative to water was similar for both groups at each observation point, suggesting that the effect of ANF was equivalent for both intakes. Thus, ANF not only inhibits water intake following water deprivation, but also inhibits both water and salt ingestion when both are required to correct a plasma volume deficit.

35.8

CARDIAC AND ARTERIAL BARORECEPTOR INFLUENCES ON DRINKING AND VASOPRESSIN SECRETION. E.W.Quillen, Jr., L.C.Keil, and I.A. REID. Dept. of Physiology, University of California, San Francisco, CA. 94143

Thoracic inferior venal caval constriction (TIVC) stimulates drinking and the secretion of vasopressin (AVP). To determine the role of the cardiac and arterial baroreceptors in these responses, observations were made in 9 sham, 10 cardiac (CD), 6 arterial (SAD), and 4 combined CD+SAD denervated conscious dogs. TIVC produced similar initial pressure reductions in all groups, with mean arterial pressure decreasing from 109±3 to 81±6 mmHg ($p<.01$), left atrial pressure from 7±1 to 2±1 cmH2O ($p<.01$), and right atrial pressure from 3±1 to -1±1 cmH2O ($p<.01$). Control plasma AVP (3.5±0.9 pg/ml) was similar in all groups. After TIVC, plasma AVP (pg/ml) increased to 68±8 in sham ($p<.01$), 31±3 in CD ($p<.02$), 53±6 in SAD ($p<.01$), and 20±3 in CD+SAD ($p<.03$). In separate experiments, water intake (ml/kg/2hr) following TIVC was 19±2 in sham dogs, and was reduced to 11±3 in CD ($p<.05$), 6±3 in SAD ($p<.05$), and 2±2 in CD+SAD dogs ($p<.01$). Plasma angiotensin II was increased similarly in all groups from 14±3 to 59±13 pg/ml. These data indicate that the baroreceptors, rather than angiotensin II, are primarily responsible for the drinking and vasopressin responses to TIVC. The cardiac and arterial baroreceptors contribute equally to the drinking response, but cardiac baroreceptors are more important than arterial receptors in the AVP response. Supported by HL 29714.

35.9

LYMPH FLOW OF THE THORACIC DUCT DURING HEAD-OUT WATER IMMERSION (WI) IN CONSCIOUS DOGS. K. Miki*+, M.M. Pazik*, E. Krasney*, S.K. Hong, and J.A. Krasney. Dept. Physiol. SUNY at Buffalo, New York 14214

WI causes a sustained fluid movement from extravascular space into plasma in dogs (Fed. Proc. 28:318, 1985). The focus of this experiment was on the contribution of lymph flow to this fluid shift. After establishing a side-fistula of the thoracic duct at least 2 days prior to the experiment, 6 splenectomized conscious dogs were studied to measure lymph flow of the thoracic duct ($\dot{q}l$), hematocrit (Hct), and plasma and lymph protein concentration during a 60 min control period in air and during a 120 min period of WI (37°C). $\dot{q}l$ during the air control period averaged 0.93±1.0 (SE) ml/min. $\dot{q}l$ tended to decrease immediately after the start of WI and then was maintained at a level averaging 0.66 ml/min during WI. The ratio of plasma protein concentration to lymph protein concentration did not change significantly. The hematocrit decreased significantly by a peak value of 1.51±0.2% (Hct unit) below control levels at 40 min of WI. Urine flow increased significantly to a maximum of 1.5± 0.5 ml/min at 40-60 min of WI compared to a mean value in air of 0.3±0.1. The Hct and urine flow responses indicate that fluid moved into the intravascular space during WI. However, $\dot{q}l$ tended to decrease. We therefore conclude that the major movement of the fluid in WI is across the capillary wall, and not via the lymph duct. (Supported by NIH-HL-28542). +Present address: Dept. Physiol., UOEH, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, 807 Japan.

35.10

CONTRASTING INFLUENCES OF NITROPRUSSIDE AND VERAPAMIL ON KIDNEY FUNCTION IN CHLORALOSE-ANESTHETIZED DOGS. J.-S. Chen*, E. F. Montgomery*, K.E. Edwards*, and A.J. Gorman. Dept. of Physiology, East Carolina Univ. Sch. of Med., Greenville, N.C. 27834.

The purpose of this study was to compare the influences of two vasoactive agents, nitroprusside (N) and verapamil (V), on renal excretory function. Mongrel dogs (N=4, 20-25 kg) premedicated with morphine sulfate (0.5 mg/kg) were anesthetized with chloralose (80 mg/kg, 0.5 mg/kg/min) given in 0.5% NaCl solution (20 ml/kg, 0.3 ml/kg/min). A priming volume of 15 ml/kg of 0.9% NaCl was also given i.v. The dogs were instrumented to measure arterial pressure (ABP) and collect bladder urine. After two 10-min control periods N (7-10 ug/kg/min i.v.) or V (180 ug/kg; 12 ug/kg/min i.v.) were infused and measurements were made during three 10-min periods. Both N and V decreased mean ABP by 12-15 mmHg from control levels of 117-125 mmHg. Basal urine flow of 4.17 ± 0.66 ml/min was significantly reduced by 67% and 62% after 10 and 30 min of N infusion, respectively. C-H2O (1.59 ± 0.27 ml/min) was reduced by as much as 135% after 30 min of N infusion. In contrast, V infusions significantly increased basal urine flow (3.23 ± 1.01 ml/min) within the first 10 min (+55%) and was 83% greater after 30 min. C-Osm (1.76 ± 0.26 ml/min) and C-H2O (1.51 ± 0.82 ml/min) were increased by 60% and 82%, respectively, during V infusion. These data show that in contrast to nitroprusside, verapamil produces significant diuresis and increases in C-Osm and C-H2O.

35.11

HYPERKALEMIA OF HYPERTONIC EXPANSION IN ANURIA: DIFFERENCES FROM HYPEROSMOLAR EXPANSION. A.H. Tzamaloukas*, J.E. Jackson* and D.A. Long* (SPON: K.D. Gardner, Jr). VA Medical Center and University of New Mexico, Albuquerque, NM.

Rapid increase in blood osmolality creates hyperkalemia. We studied the effect of the solute species responsible for the hyperosmolality of this hyperkalemia by infusing into anuric female dogs comparable amounts (11-15 mosm/kg) of 0.85 m NaCl (group A, n=6), 1.6 m mannitol (gr. B, n=5), or 50% ethanol in NaCl (gr. C, n=3). Control anuric dogs were infused with isotonic NaCl (gr. D, n=6), isotonic NaCl plus 12 m KCl (gr. E, n=5), or no infusion (gr. F, n=4). ECF expansion was equal in groups A, B, D and E. Results: Osmolality (mosm/kg), gr. A. control (i) 315±5, immediately post infusion (ii) 346±6, 60 min post infusion (iii) 340±5. Gr. B, (i) 316±6, (ii) 341±7, (iii) 336±6. Gr. C, (i) 290±2, (ii) 344±9, (iii) 310±2. Gr. D, (i) 307±6, (ii)309±8, (iii) 312±2. Gr. E, (i) 309±8, (ii) 308 ±8, (iii) 310±9. Gr. F, (i) 315±7, (ii) 316±8, (iii) 315±7. Serum potassium (mmol/l), gr. A, (i) 3.4±0.3, (ii) 3.7±0.3, (iii) 4.4±0.4. Gr. B, (i) 3.5±0.3, (ii) 4.3±0.3, (iii) 4.6±0.5. Gr. C, (i) 3.6±0.4, (ii) 3.3±0.4, (iii) 3.3±0.3. Gr. D, (i) 3.7± 0.1, (ii) 3.4±0.2, (iii) 3.7±0.2. Gr. E, (i) 3.6±0.2, (ii) 4.3 ±0.3, (iii) 4.1±0.5. Gr. F, (i) 3.3±0.3, (ii) 3.5±0.3, (iii) 3.7±0.3. Serum potassium rose significantly post infusion only in groups A, B and E. Conclusion: Acute hyperosmolality from solute excess creates hyperkalemia only if the excess solute has extracellular, not total body water, distribution.

35.12

SUPPRESSION OF DEPLETION-INDUCED SALT APPETITE BY THE TACHYKININS. M. Massi*, G. de Caro*, R.R. Sakai*& A.N. Epstein, Univ. of Camerino, Italy & Univ. of Pennsylvania, Phila. Pa. 19104.

Tachykinin peptides, which are of non-mammalian origin (eledoisin, physalaemin, kassinin) and are present in mammalian brain (substance P, neurokinin alpha, eledoisin & physalaemin like immunoreactivity), suppress salt intake elicited by acute sodium depletion (SC furosemide and removal of ambient Na followed by 2 hr access to 3% NaCl). When given in doses of 100-4000 ng by pulse intracerebroventricular (ICV) injection to depleted rats just prior to salt access, their order of potency is: eledoisin > kassinin > physalaemin > substance P > neurokinin alpha. Eledoisin was therefore chosen for continuous ICV experiments and was exceptionally potent, producing 90% suppression of intake at 10 ng/min/rat and 50% at as little as 0.01 ng/min/rat with orderly decreases in suppression at intermediate doses. In contrast to the susceptibility of salt intake to suppression by ICV tachykinins, food intake was resistant. Solid food consumption (18 hr deprivation) was unaffected by the same pulse ICV doses of the tachykinins with the exception of high doses of eledoisin which suppressed intake, but only for 15 min, because of excessive grooming. Milk intake was increased by 100 ng of kassinin and unaffected by 500 ng. The tachykinins, especially those that are endogenous to the brain, may be natural inhibitors of salt intake. Supported by NATO RG 0502, NS 03469, and the MacArthur Foundation.

35.13

**PRE- AND POST-INGESTIONAL FACTORS IN ANGIOTENSIN II INDUCED DRINKING.** **J.J.Salisbury*, N.E.Rowland and M.J.Fregly Univ of Florida, Gainesville, FL 32611**

**Rats treated with angiotensin II (AII) drink more 0.15M NaCl than water in single-bottle tests. In order to determine whether this is due to post-ingestional factors or taste, male rats were fitted with both intravenous (IV) and intragastric (IG) catheters. They were then infused IV with AII (125 ng/min) and, during elicited bouts of water intake, they received IG injections of 1.5M NaCl (0.1 ml per ml water taken orally). This procedure results in 0.15M NaCl at the level of the stomach, yet the water intake in this condition did not differ from that in control conditions in which either water or nothing were infused IG. This suggests that it is not postingestive effects, but is the taste of NaCl that facilitates drinking in response to AII. However, in a second experiment in which rats were fitted with gastric drainage fistulas, postingestive effects of water also appeared important. Thus, rats drank more water during IV AII infusion when the fistula was open (sham drinking condition) than when the fistula was closed. Intake increased with successive trials in the open condition, without any change in response during fistula closed tests. Sham drinking of 0.15M NaCl was also increased in the open condition. Support: NHLBI grant HL 14526.**

35.14

CHANGES IN ABSORPTIVE RATES IN THE RAT INTESTINES IN RESPONSE TO VOLUME DEPLETION AND EXPANSION. Thomas B. Landry and Roberta M. O'Dell-Smith* University of New Orleans, New Orleans, LA 70148.

The rates of absorption in isolated segments of the jejunum, ileum and colon of the rat intestine were measured using a technique devised by Bresler et al. (Am. J. Physiol. 239:F466-F473, 1980) which allows for an in vivo examination of absorptive rates and permits the three segments to be studied in a single rat, eliminating the need for many controls. Absorptive rates plateaued at a constant level at approximately 70 minutes with 2.28 µl/min jejunum, 2.17 µl/min ileum and 2.48 µl/min colon representing an average of 14 experiments using 3cm segment lengths. Once plateau values were reached, the rats were volume depleted by removal of 2ml of blood from the jugular vein. There was a sharp rise in the absorptive rate in the jejunum to 2.70 µl/min. The ileum remained fairly constant and the colon decreased to an average constant level of 1.53 µl/min after 15 min. Six rats were expanded by injection of 2ml of normal saline in a single bolus into the jugular vein. In all three segments there was a slight decrease in absorptive rates followed by a return to original values in 25 min. These data are consistent with those of Bresler et al. who found an increase in absorptive pressure with volume depletion in the jejunum and a decrease of absorptive pressure in volume expansion.

36.1

WORLDWIDE DISTRIBUTION OF 131-I IN ANIMAL THYROIDS AFTER REACTOR ACCIDENT AT CHERNOBYL, USSR. L. Van Middlesworth and Ulrich Loos*. University of Tennessee, Memphis, TN 38163, Universitat Ulm, Ulm, West Germany

For 32 years bovine and ovine thyroid glands have been sent to this laboratory every 2-4 weeks for analyses of radioiodine content. Following the nuclear reactor accident at Chernobyl, USSR on April 26, 1986, the following data were accumulated. There was no measurable 131-I (<0.1 pCi/g) in bovine glands from Ulm, Germany 3 days after the accident and none in ovine thyroids from Birmingham, England on the 4th day after the accident. By the 8th day, glands from Ulm contained 2,000 pCi 131-I/g which increased to 15,000 on the 13th day and 33,000 on the 24th day. Similarly, the ovine glands from England contained 9,500 pCi 131-I/g on the 24th day. Japanese cattle thyroids showed their first 131-I as 15 pCi on the 9th day; this increased to 75 pCi/g on the 25th day. In Tennessee, 2.5 pCi/g appeared on the 16th day and increased to 140 pCi/g on the 30th day. These data suggest that milk in Ulm would have contained more than 4,000 pCi 131-I/l within 3 weeks after the accident which should have resulted in more than 1.5 rem of beta and gamma radiation to the thyroids of young children consuming milk in Ulm; this dose would be biologically inconsequential. It is suggested that many children drinking milk and living 1,000 miles closer to the accident may have received thyroid ablative doses of 131-I, in addition to short-lived isotopes of iodine.

36.2

HORMONAL AND ELECTROLYTE RESPONSES OF CONSCIOUS SHEEP TO 96 HRS OF NORMOBARIC HYPOXIA. D. Curran-Everett*, J.R. Claybaugh, S.K. Hong and J.A. Krasney. Dept. Physiology, SUNY-Buffalo, Buffalo, NY and Dept. Clin. Invest., Tripler AMC, Honolulu, Hawaii 96859.

Hypoxia alters the relationship of plasma renin to aldosterone. The potential role plasma electrolytes play in this apparent dissociation is not clear. This study evaluated the interrelationships of renin, aldosterone, and plasma electrolytes during 96 hrs of normobaric hypoxia. Eight (8) adult ewes were exposed to hypoxia by $N_2$ dilution in an environmental chamber ($PaO_2$ = 40 torr). Urine (Foley catheter) and arterial plasma samples were assayed for Na, K, renin (RIA), and aldosterone (RIA). Plasma Na and K remained unchanged ($p>0.15$). The sheep were in negative K balance at 96 hrs of hypoxia ($p<0.01$) secondary to decreased K intake. However, the sheep remained in Na balance ($p=0.5$). Although GFR and fractional Na excretion did not change ($p>0.1$), fractional K excretion decreased ($p<0.001$). Plasma renin activity increased 150%. Aldosterone excretion (ng/mg cr) progressively decreased to 25% of normoxic levels by 72 hrs of hypoxia. The decreased aldosterone excretion in these conscious ewes may be consistent with a suppression of aldosterone secretion which may result in the increased fractional reabsorption of $K^+$. Supported by HL-24683, HL-28542 and HL-36126 from NHLBI and U.S. Army Research and Development Command.

36.3

THE AROUSAL RESPONSE FROM SLEEP TO RAPIDLY DEVELOPING HYPOXEMIA IN LAMBS: THRESHOLD AND LATENCY. James E. Fewell, Susan B. Baker*. UAMS, Little Rock, Ar. 72205

Experiments were done to investigate the arousal response from sleep to rapidly developing hypoxemia (H) in eight lambs. Each lamb was anesthetized and instrumented for recordings of ECoG, EOG, nuchal and diaphragm EMGs and measurements of O2 saturation (fiberoptic catheter oximeter). A tracheotomy was done and a tracheostomy tube placed in the trachea so that the FIO2 could be changed quickly. No sooner than 3 days after surgery, measurements were made in quiet sleep (QS) and active sleep (AS) during a control period when the animal was breathing 21% O2 and during an experimental period of H when the animal was breathing either 10%, 5% or 0% O2. The results were:

| Sleep State | #Epochs Aroused | Time to Arousal | Control O2 Saturation at Arousal |
|---|---|---|---|
| QS-10%O2 | 22/22 | 44±43 sec | 92±3----------80±7 |
| QS-5% O2 | 25/25 | 13±9 sec | 92±4----------81±5 |
| QS-0% O2 | 26/26 | 6±2 sec | 92±4----------83±5 |
| AS-10%O2 | 19/19 | 70±53 sec | 92±4----------76±6 |
| AS-5% O2 | 21/23 | 44±15 sec | 91±4----------54±10 |
| AS-0% O2 | 13/23 | 21±5 sec | 92±4----------46±12 |

During QS, arousal occurred once an arousal threshold was reached; however, during AS, there was an arousal latency once the arousal threshold was reached. Furthermore, during some epochs of AS, electrocortical signs of cerebral hypoxia and primary apnea occurred before arousal.

36.4

THE EFFECT OF GENDER ON THE RESPONSE TO LOWER BODY NEGATIVE PRESSURE. D.L. Hudson*, M.L. Smith, P.B. Raven. Dept. of Physiology, Tex. Coll. Osteo. Med., Fort Worth, TX 76107.

Previous reports have indicated that women were less tolerant than men to sudden onset lower body negative pressure (LBNP). However, the components of blood pressure regulation which would account for this gender difference has not been identified. In the present study, sixteen females and twenty males (mean age=26±2.1 years) were evaluated during progressive LBNP to -50 torr. Nine male subjects suffered pre-syncopal symptoms at -50 torr LBNP while none of the female subjects experienced pre-syncopy. Calculated forearm vascular resistance (FVR), heart rate (HR), and blood pressure (SBP) were determined during LBNP. Mean change (Δ) from 0 to -50 torr LBNP for selected measurements and for the calculated index of baroreflex function were as follows (* $p<.05$):

| | ΔHR (beats/min) | ΔSBP (torr) | ΔFVR (torr/[ml/min/100ml]) | ΔHR/ΔSBP |
|---|---|---|---|---|
| F | +24 | -16* | +45.6* | 1.66* |
| M | +23 | -19 | +17.7 | 1.30 |

These data indicate that the female subjects had a greater vasoconstrictor response and baroreflex responsiveness than the males during progressive LBNP. This observation appears related to the greater orthostatic tolerance observed in the female.

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36.5

EVENING BRIGHT LIGHT CAN PHASE DELAY THE HUMAN CIRCADIAN PACEMAKER INDEPENDENT OF THE TIMING OF THE SLEEP-WAKE CYCLE. C.A. Czeisler, J.S. Allan*, S.H. Strogatz*, J.M. Ronda*, R. Sanchez*, C.D. Rios*, W.O. Freitag*, G.S. Richardson*, and R.E. Kronauer*. Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115.

We report a controlled case study demonstrating that critically timed exposure to bright indoor light can rapidly reset the human circadian pacemaker by about six hours, even when the timing of the sleep-wake cycle is held constant. A 66 year old woman with a marked phase advance of the circadian pacemaker relative to sleep was selected for study on the hypothesis that a region of the circadian cycle sensitive to phase shifts by light would occur during normal waking hours. Bright indoor light was administered for four hours on seven consecutive evenings. Comparison of control, baseline, and post-intervention measurements of core body temperature and serum cortisol showed that the light exposure caused an unexpectedly large six hour phase delay shift of the circadian pacemaker with respect to both clock hour and sleep, occurring largely on the first day. It thus appears that light acts directly on the circadian pacemaker in a manner characteristic of other mammalian species, rather than through an intermediary process such as modification of the sleep-wake cycle. It is expected that bright light will find greater application to the treatment of insomnia, jet-lag, affective disorders, and other disorders of known or presumed circadian etiology.

36.6

CHANGES IN ESOPHAGEAL AND ARTERIAL BLOOD PRESSURE DURING L-1 STRAINING MANEUVERS AND FATIGUING ISOMETRIC CONTRACTIONS. C.A. Williams, J.E. Douglas, G. Miller, R.L. Wiley and A.R. Lind Dept. of Physiology, College of Medicine, East Tennessee State Univ., Johnson City, TN 37614

Changes in esophageal pressure (Peso), blood pressure (BP), and heart rate (HR), were measured during brief (15sec) L-1 straining maneuvers and fatiguing isometric contractions of the handgrip and quadriceps on 9 male subjects. This was done in order to determine what, if any, contribution increases in intrathoracic pressure had on the pressor response to isometric exercise. During the L-1 maneuver, Peso increased abruptly to 117± 5 mmHg but then fell by 35 mmHg within the initial 5 sec period of straining. HR increased steadily during the L-1 efforts, reaching peak levels of 132 ±5 bpm at the end of the maneuver. MBP increased initially to 195 ± 5 mmHg, but fell by 30-35 mmHg within the first 5sec of the maneuver. In contrast, during fatiguing isometric contractions, there was no sustained pattern of breath holding and Peso at expiration gradually increased, reaching peak levels at fatigue of 40 ±6 mmHg. HR increased by 45-60 bpm. MBP increased steadily throughout the exercise, peaking at 195-205 mmHg at fatigue. These data suggest that the changes in BP during the L-1 are due to the large positive intrathoracic pressure generated during the straining but the BP during isometric exercise could not be accounted solely on the basis of changes in Peso. (AF grant F33615-81-C-0500)

## 36.7

INTERVAL TRAINING INCREASES THE VASCULAR TRANSPORT CAPACITY OF RAT HINDLIMB MUSCLES. W.L. Sexton, R.J. Korthuis, and M.H. Laughlin. Dept. of Biomedical Sciences and Dalton Research Center. Univ. of Missouri, Columbia, MO 65211.

The purpose of this study was to determine if high-intensity interval training (IT) increases the vascular transport capacity of the hindlimb muscles in the rat. Male Sprague-Dawley rats (n=14) were IT 5 days/week at 60 m/min on a 15% grade for 8 weeks, while a control group (n=14) was cage confined. IT consisted of 6 bouts of alternating running (2.5 min) and recovery (4.5 min). The vascular transport capacity was evaluated by measuring the total flow capacity (at 4 perfusion pressures) and the capillary filtration coefficient (CFC) in isolated, maximally dilated (papaverine) hindquarters perfused with Tyrode's solution containing 5% albumin. Although isogravimetric capillary and perfusion pressures for C and IT rats were not different, the isogravimetric flow was higher and the total vascular resistance ($R_T$) was lower in the IT rats. The decreased $R_T$ was a result of reductions in both the pre-(Ra) and post-capillary (Rv) vascular resistances. Furthermore, these changes were associated with an increase in CFC, suggesting that the functional microvascular surface area was increased in IT rats. The Ra/Rv ratios for C and IT groups were not different. The vascular flow capacity at elevated perfusion pressures averaged 41% greater in the IT group. These data suggest that IT increased the vascular transport capacity in these rats by increasing both the vascular flow capacity and the functional surface area of the hindquarters. (Supported by NIH grants HL36088 and HL36069.)

## 36.8

CONCOMITANT STRENGTH AND ENDURANCE TRAINING MAY AFFECT PEAK TORQUE IN KNEE EXTENSION AND FLEXION. R.L. Pohlman, L.A. Darby, and R.L. Bartels*, Division of HPR, Wright State University, Dayton, OH 45435, Department of HPE, Austin Peay State University, Clarksville, TN 37044, and Laboratory of Exercise Physiology, The Ohio State University, Columbus, OH 43210.

Twenty-one previously sedentary women participated in a 7-week isokinetic strength (S), endurance-run (E), or combination isokinetic and endurance-run training program (SE). The (S) group performed 2 sets of 8 repetitions of knee flexion and extension three times per week on the Orthotron, while the (E) group completed a walk-jog regimen increasing each week 15% of total mileage. The (SE) group completed both types of training. Relative max and $\dot{V}O2$ significantly increased 18.3% and 26.0% in the (SE) and (E) groups, respectively. Peak torque values for dominant leg measured on the Cybex II dynamometer significantly increased for knee flexion pre- to post-training in the (S) [$\bar{X}$ ± SEM (Nm): $60^{0}$/s = 88.5 ± 5.3; $180^{0}$/s = 70.0 ± 3.9; $270^{0}$/s = 54.6 ± 3.4] and (E) [$\bar{X}$ ± SEM (Nm): $60^{0}$/s = 86.2 ± 7.1; $180^{0}$/s = 65.6 ± 6.9; $270^{0}$/s = 52.1 ± 4.3] groups while (SE) group values did not change. At $60^{0}$/s leg extension, post-training values for the (S) and (E) groups were significantly different from the (SE) group [$\bar{X}$ ± SEM (Nm) : (S) = 135.2 ± 8.0; (E) = 130.3 ± 11.3; (SE) = 116.6 ± 4.9]. Total body weight, and body composition were not significantly different pre- to post-training. Although aerobic capacity was not affected by the combination training, the lack of improvement in (SE) group peak torque values suggests conflict between concomitant strength and endurance adaptions.

## 36.9

THE EFFECTS OF ANAEROBIC AND AEROBIC TRAINING ON THE APPETITE, FOOD INTAKE AND BODY COMPOSITION OF UNTRAINED WOMEN. L.A. Darby, R.L. Pohlman, V.M. Vivian* and R.L. Bartels. Depart. HPE, Austin Peay State University, Clarksville, TN 37040, Div. HPR, Wright State University, Dayton, OH 45435, and Laboratory of Exercise Physiology, The Ohio State University, Columbus, OH 43210.

Fourteen untrained college women, 20-26 years of age, participated in an aerobic walk-jog or anaerobic interval training program. Food intake records listing all food consumed daily were collected on Tuesdays and Wednesdays one week prior to, during, and one week after the six week training period. Appetite was operationally defined for this study as the responses of the subjects to a hunger perceptions questionnaire given before and after the training period. The body composition, maximal oxygen consumption, Margaria-Kalamen power test value, and body weight of each subject were determined before and after training. Maximal oxygen consumptions of the anaerobic and aerobic groups increased pre- to posttraining by 19.9% and 15.8%, respectively. Although the aerobic fitness level of each group improved, there were no significant changes in total energy, protein, fat, or carbohydrate intakes after regression and covariate analyses were calculated. Additional physiological parameters evaluated by between-within two-factor mixed design ANOVAs, and paired and unpaired $t$-tests also did not change significantly. It was concluded that moderate exercise, regardless of type, did not affect the appetite, food intake, or diet composition of previously untrained women.

## 36.10

CARDIO-RESPIRATORY RESPONSE TO ONE YEAR OF AEROBIC EXERCISE OR STRENGTH TRAINING IN POST-MENOPAUSAL WOMEN. C. Fields*, C.W. Zauner, A.D. Martin*, M. Notelovitz*, The Center for Climacteric Studies, Inc., Gainesville, Florida, 32601.

Seventy-three asymptomatic post-menopausal women of normal ht/wt ratios, ages 45-73 ($\bar{X}$=58.1), were randomly assigned to Nautilus resistance training, treadmill walking or bicycle ergometry. Nautilus subjects were trained to muscular failure for all major muscle groups, while treadmill and bicycle groups trained at 70-85% of maximum heart rate (HRmax). All groups trained three times/week for 20 minutes. A fourth group of volunteers served as non-exercising controls. Significance was accepted at $p<0.05$. While there were no differences between treadmill and bicycle groups, the aerobically trained groups showed significant improvement over the Nautilus and control groups in maximum oxygen uptake ($\dot{V}O_2$max) and total exercise time (TET) at 3 and 6 months. The Nautilus group had a significant increase in TET at 6 months, but no change in $\dot{V}O_2$max. Body weight for the Nautilus group increased from 0-3 months. Although treadmill and bicycle subjects trained only 60 minutes/week for one year at an intensity of 70-85% HRmax, they evidenced increases in $\dot{V}O_2$max of 12% and 9% while TET increased 19% and 13% in each case. Nautilus subjects showed an increase of 3% in $\dot{V}O_2$max and 8% in TET. Increased TET with no corresponding increase in $\dot{V}O_2$ suggests improved biomechanical efficiency in the resistance training group. Research supported by Nautilus Sports Medical Industries, Inc.

## 36.11

MEASUREMENT OF OXYGEN UPTAKE IN THE NON-STEADY-STATE. S.K. Powers, J. Lawler*, D. Thompson*, and R. Beadle*. Applied Physiology Laboratory, School of HPERD, LSU, Baton Rouge, LA 70803.

The purpose of these experiments was to develop and validate an open-circuit technique for measurement of gas exchange during the transition from rest to constant load steady-state exercise. The design of the open-circuit system employed to measure gas exchange in these experiments used a mixing chamber to collect the subject's expired gas. In calculating $\dot{V}O_2$, the mixed expired gas concentrations were matched with ventilatory volume using a previously determined time delay. To determine the validity of the open-circuit system, four subjects performed 16 rest to work transitions. In eight of the experiments, serial measurements of $\dot{V}O_2$ were obtained every 20-seconds for 3-min using the open-circuit mixing chamber system while the additional eight experiments used the Douglas bag technique. No significant difference ($p>0.05$) existed between $\dot{V}O_2$ values calculated by the two techniques. Mean differences in $\dot{V}O_2$ between the two techniques during the first three 20-second measurement periods were 6, 53, and 63 ml, respectively. Using the Douglas bag technique as the standard, this represents a relative measurement error of 0.1%, 4.5% and 3.6%, respectively, at the above time intervals. These data demonstrate that an open-circuit system employing a mixing chamber and the appropriate time delay to match expired gas fractions and ventilation is a sensitive means of measurement of $\dot{V}O_2$ in the non-steady-state.

37.1

EFFECTS OF CHANGES IN TEMPERATURE AND INSPIRED $CO_2$ ON THE BREATHING PATTERN OF TURTLES (Chrysemys picta). W.K. Milsom and G.D. Funk. Department of Zoology, University of British Columbia, Vancouver, B.C, Canada

Respiratory minute ventilation ($\dot{V}_E$), breathing pattern, oxygen consumption ($\dot{V}_{O2}$) and arterial blood gases and pH were measured in freshwater turtles (Chrysemys picta) at 10, 20 and 30°C while the animals breathed gases of varying $CO_2$ concentration ($F_{ICO2}$ = 0, 2, 4, 6 and 8%). Increasing body temperature produced unequal increases in $\dot{V}_E$ and $\dot{V}_{O2}$ such that $\dot{V}_E/\dot{V}_{O2}$ decreased. This relative hypoventilation led to a rise in $Pa_{CO2}$ and fall in pHa. Increasing $F_{ICO2}$ at all temperatures greatly elevated $\dot{V}_E$. The magnitude of this response increased with increasing temperature. Thus, paradoxically, there was an increase in both $Pa_{CO2}$ and $CO_2$ sensitivity with increasing temperature. The changes in breathing pattern due to increasing temperature and increasing $F_{ICO2}$ were different. Increases in $\dot{V}_E$ due to increases in temperature were primarily due to a shortening of the periods of breath holding. With increases in $F_{ICO2}$ there was an increase in $V_T$ and in the number of breaths per bout of breathing as well as a decrease in the periods of breath holding. In relative terms, increasing temperature had no effect on the $CO_2$ response of any respiratory variable. Analysis of the data indicates that all changes which occurred in $\dot{V}_E$, $Pa_{CO2}$ and pHa with changes in body temperature can be explained by equal $Q_{10}$ effects of roughly two on both metabolic rate and ventilatory sensitivity to changes in $Pa_{CO2}$.

Supported by the NSERC of Canada.

37.2

EXTRAPULMONARY GAS TRANSPORT TO BRAIN IN ANESTHETIZED PIGEONS: EFFECTS OF TEMPERATURE AND HYPOXIA Shawn D. Pierce* and Marvin H. Bernstein, New Mexico State Univ. Las Cruces, NM 88003

Extrapulmonary enhancement of the cerebral $O_2$ supply occurs in birds when blood perfusing nasal mucosa acquires $O_2$ across nasopharyngeal surfaces and transfers it to cephalic arterial blood via countercurrent exchange within the rete ophthalmicum (RO), a network of arteries and veins that also functions in regulating brain temperature ($T_b$). To illuminate the operation of this exchange system we inserted a ventilated T-cannula into the trachea of pigeons (Columba livia, mean mass 0.7 kg) via the glottis, isolating respiratory from nasopharyngeal surfaces. Pure $H_2$ gas blown through the nasal cavities only of halothane-anesthetized birds appeared at a Pt electrode in the hypothalamus but not in the systemic circulation. Breathing of $N_2$-diluted air ($PO_2$ of air at 5 km above sea level) caused $H_2$ to appear faster in the brain. When body temperature ($T_c$) was reduced during hypoxia the body-brain temperature difference ($dT = T_c - T_b$) decreased, and the rate of $H_2$ appearance in the brain slowed. Increased $T_c$ during hypoxia had the converse effects. The data suggest that the increased dT previously observed in exercising birds, probably due to increased arterial cooling in the RO, may be accompanied by increased extrapulmonary gas exchange between the nasopharynx-RO complex and the brain. This would enhance the cerebral $O_2$ supply during flight, and might be especially important at high altitude. (Supported by NSF grant DCB-8402659.)

37.3

BLOOD GAS AND CARDIOVASCULAR CHANGES IN EXERCISING BAR-HEADED GEESE BREATHING NORMOXIC AND HYPOXIC GASES. M.R. Fedde, J.A. Orr, H. Shams* and P.Scheid. Kansas State Univ., Manhattan, KS 66502, Univ. Kansas, Lawrence, KS 66045, and Ruhr Univ., Bochum, FRG.

Bar-headed geese (Anser indicus) are extremely tolerant of hypoxic environments. We measured blood gases in arterial (Pa), mixed venous ($P\bar{v}$), and venous blood ($P_1$) (from a leg) in these birds during treadmill exercise (0.6 m/sec at 2° incline) while they breathed either 21% or 7% $O_2$. While breathing 21% $O_2$, $PaO_2$ was unchanged by exercise but $PaCO_2$ was lowered about 8 torr. During exercise, $P_1O_2$ was reduced 11 torr and $P_1CO_2$ 1 torr from that at rest. $P_1O_2$ was not lower than $P\bar{v}O_2$. Exercise caused increases in cardiac output (Q) of 91%, and heart rate (HR) of 128%, while mean arterial blood pressure (MABP) remained essentially unchanged; stroke volume (SV) and total peripheral resistance (TPR) decreased by 17 and 42%, respectively. While breathing 7% $O_2$, $PaO_2$ increased from 28 to 34 torr during exercise and $PaCO_2$ decreased from 18.7 to 13.3 torr. $P_1O_2$ was not reduced below $P\bar{v}O_2$ (18 torr) during exercise. Hypoxic exercise limited increases in Q to 19%, while HR still increased 78% and MABP increased 29% but TPR increased 31%; SV decreased 31%. Although complex changes in the cardiovascular system accompany exercise during hypoxia, increases in blood flow appear to limit the changes in blood gases in blood leaving the exercising muscles. Supported by NSF Grant 83-20260.

37.4

EFFECTS OF HYPOBARIC HYPOXIA ON BLOOD $O_2$ TRANSPORT IN PIGEONS. L.A. Maginniss, M.H. Bernstein, M.A. Deitch*, and B. Pinshow. Div. of Biol. and Med., Brown Univ., Providence, RI 02912 and Dept. of Biol., New Mexico State Univ., Las Cruces, NM 88003.

Two groups of adult Columba livia were investigated. High altitude pigeons (HA) were acclimated for 6 wk at 7 km simulated altitude (308 torr, 25°C); sea level birds (SL) were maintained for 5 - 6 wk at 758 torr (25°C). Isocapnic $O_2$ equilibrium curves were measured for both animal groups at 37° and 41°C using thin blood film techniques. At pH 7.50 and 41°C, the half saturation $P_{O2}$ ($P_{50}$) for HA and SL pigeons were 32.9 ± 1.4 (6) and 35.6 ± 0.6 (6) torr, respectively. This affinity difference was not caused by changes in isohemoglobin composition; isoelectric focusing techniques revealed similar isoHb profiles for both animal groups. Hill plots showed no differences in equilibrium curve shape for HA and SL birds. Furthermore, both animal groups exhibited similar Hb-$O_2$ temperature coefficients ($\Delta \log P_{50}/\Delta°C$ = .022 - .024) and $CO_2$ Bohr slopes ($\Delta \log P_{50}/\Delta pH$ = -.41). Hypoxic acclimation elicited a significant polycythemia; hematocrit and [Hb] increased by 38% and 43%, respectively. We conclude that the altitude tolerance of pigeons is enhanced by the temperature- and pH-independent reduction of $P_{50}$, the increased blood $O_2$ carrying capacity, and the effect of hypoxia-induced hypothermia on $O_2$ affinity. At an arterial $P_{O2}$ of 30 torr, calculated in vivo $Ca_{O2}$ for HA (39.2°C, pH 7.53) and SL (41°C, pH 7.50) birds were 14.2 and 7.6 vol%, respectively. Supported by NSF PCM-8202702 (LAM) and NSF DCB-8402659 (MHB).

37.5

VENTILATORY AND ACID-BASE RESPONSES TO ANOXIC GAS BREATHING IN THE TURTLE, CHRYSEMYS PICTA BELLII. Jeremy S. Wasser* and Donald C. Jackson. Brown Univ., Providence, RI 02912.

We exposed turtles to 6 hours of anoxia by having them breathe 1 of 3 anoxic gas mixtures (95%N2-5%CO2, 98.5%N2-1.5% CO2, 100%N2). We monitored Ve, f, Vt, VO2, and VCO2, and measured hematocrit, pHa, PaO2, PaCO2, and arterial [$HCO_3^-$], [lactate$^-$], [Na], [K], [Ca], [Mg], and [Cl] at control (room air), 1, 2, 4, and 6 hours of anoxia and 1 hour of recovery. In all 3 protocols, turtles hyperventilated with a peak Ve occurring after 1 hour of anoxia. Ve then decreased but remained above control values after 6 hours. During recovery Ve quickly increased to 8-13 times control. PaCO2 rose from control values of 23.6 and 28.2 mmHg to 49.7 and 39.0 mmHg after 6 hours of exposure to 95%N2-5%CO2 and 98.5%N2-1.5%CO2 respectively and fell from 24.6 mmHg to 21.1 mmHg after 6 hours of exposure to 100%N2. Plasma [Na] remained constant while [Ca], [Mg] and [K] increased and [Cl] decreased slightly over the 6 hours for all 3 gases. Plasma strong ion difference decreased due to increasing [lactate$^-$] that was only partially compensated for by the small change in other strong ions. We found no obvious correlation between acid-base variables and the degree of hyperventilation with anoxic gas breathing. We conclude that the increase in Ve observed is due primarily to anoxia and not to changes in acid-base state. The decrease in Ve after 1 hour of anoxia may be due to an acid-base mediated metabolic depression but the control mechanism remains obscure.
Supported by NSF Grant DCB85-02636.

37.6

IN VITRO ION EXCHANGE PROCESSES BETWEEN TURTLE SHELL AND HYPERCAPNIC SOLUTIONS. Randi B. Silver* and Donald C. Jackson Div. Biol.& Med.,Brown Univ., Providence, R.I. 02912.

Passive ion exchange occurring in vitro between shell of the turtle, Chrysemys picta bellii, and a turtle Ringer's solution was measured in response to hypercapnia and compared to previous in vivo studies. Ringer's solution (100 ml) and shell fragments (10 g) were equilibrated at 20°C with 4% $CO_2$ (control) for 24 h and then with either 7.4, 15 or 30% $CO_2$ (hypercapnia) for 72 h. Solution pH and concentrations of $TCO_2$, $Ca^{++}$, TCa, TMg, $K^+$, $Na^+$, $Cl^-$ were determined daily. $TCO_2$ increased in response to hypercapnia, but as in in vivo studies, the increase could not be accounted for quantitatively by an increase in S.I.D. Relationships between $Ca^{++}$ and TCa were linear functions of pH; the greatest changes in $Ca^{++}$ and TCa were observed at the lowest pH (highest $PCO_2$). The ratio of $Ca^{++}$ to TCa remained fairly constant during acidosis ($\Delta Ca^{++}/\Delta pH$=-2.1 mMol/unit pH, $\Delta TCa/\Delta pH$=-2.1). The in vitro relationship between Ca and pH was similar to previous in vivo data. The slope of $\Delta Ca^{++}/\Delta pH$ was the same; however, $\Delta TCa/\Delta pH$ was greater in vivo (-3.0) due to binding of Ca to $Pr^-$. These findings suggest release of Ca from shell during hypercapnia is based on passive equilibrium between plasma pH and $Ca^{++}$.
Supported by NSF DCB 8502636.

37.7

FUNCTIONAL ANALYSIS OF PULMONARY GAS TRANSPORT IN THE LIZARD, Varanus niloticus. James W. Hicks*, Atsushi Ishimatsu* and Norbert Heisler*. (SPON: F.N. White). Abteilung Physiologie, Max-Planck Institut fuer Experimentelle Medizin, Goettingen, F.R.C.

Quantitative analysis of gas transport is characterized by the models of Piiper and Scheid. The processes involved (ventilation, perfusion, diffusion) are considered in terms of conductances (G) and the performance of the system in terms of the relative resistances ($\Delta p$) and the various conductances of each process. Nine specimens of the nile monitor lizard, Varanus niloticus, were chronically prepared for both gas and blood analysis. Non-occlusive cannulae were placed into right and left atrium, right and left aortic arch and pulmonary artery. Animals were allowed to recover for 72 hours and all parameters required for the analysis were measured at 25 and 35°C. In vitro $O_2$ and $CO_2$ dissociation curves were also constructed at both temperatures. The pulmonary system of varanids exhibits an extremely low total conductance (Gtot), being only 1/100 of values reported for dog and hen. Gdiff/Gvent (diffusion/ventilation) values were found to be lower for $CO_2$ than for $O_2$. Diffusion limitation indices, Ldiff, show relatively high values compared to dog and hen values, particularly for $CO_2$, indicating large ventilation/perfusion mismatching, intrapulmonary shunts and/or diffusion resistances within the lung.

37.8

BLOOD-RECTAL TEMPERATURE DIFFERENCES AND BLOOD GASES DURING EXERCISE. J. H. Jones, C. R. Taylor, A. Lindholm*, R. Straub*, H. Hoppeler*, K. E. Longworth*, and R. H. Karas*. C. F. S., Harvard University, Old Causeway Road, Bedford, MA 01730

Exercise near maximal aerobic capacity ($\dot{V}O2max$) reportedly causes equine PaO2 to fall to nearly 60 mmHg, suggesting that these animals experience pulmonary diffusion limitation. To evaluate this phenomenon we collected blood samples from horses (460 kg) running at speeds up to those which elicited $\dot{V}O2max$ (16.6 W/kg) and simultaneously monitored temperatures with Cu-constantan thermocouples in the pulmonary artery (Tpa), 20 cm deep in the rectum (Tr) and 2.5 cm deep in the middle gluteal muscle (Tgm). Temperature differences between rectum and other sites (Tpa-r and Tgm-r) at the end of 6 min, and their effects on PaO2, were (in °C and mmHg):

| % $\dot{V}O2max$ | Tpa-r | Tgm-r | $\Delta$PaO2 (Tpa-r) | $\Delta$PaO2 (Tgm-r) |
|---|---|---|---|---|
| 35 | 0 | 0.7 | 0 | 1.8 |
| 78 | 1.3 | 1.8 | 8.7 | 12.2 |
| 96 | 2.1 | 2.6 | 12.4 | 15.6 |

Large errors in PaO2 result from correcting blood gas values to Tr, rather than the site at which gas exchange occurs: lung (Tpa) or muscle (e.g., Tgm). Supported by NSF PCM-83-17800.

37.9

SCALING PULMONARY DIFFUSION WITH BODY MASS IN MAMMALS. K. E. Longworth*, J. H. Jones, J. E. P. W. Bicudo*, R. H. Karas*, and C. R. Taylor. C. F. S., Harvard Univ., Old Causeway Rd., Bedford, MA 01730

The disparate scaling between pulmonary diffusing capacity for oxygen ($DLO2 \propto Mb^{1.0}$) and maximal rate of oxygen consumption ($\dot{V}O2max \propto Mb^{0.8}$) with body mass (Mb) indicates that smaller mammals must have a larger diffusion head for O2 ($\Delta$PO2) at $\dot{V}O2max$ than do larger mammals. To determine how $\Delta$PO2 is increased we have collected data at $\dot{V}O2max$ in four species ranging over two orders of magnitude in Mb:

| Species | Mb (kg) | $\dot{V}O2max$ (W/kg) | PaCO2 (mmHg) | PAO2 (mmHg) | PcO2 (mmHg) | $\Delta$PO2 (mmHg) |
|---|---|---|---|---|---|---|
| Fox | 4 | 72 | 19 | 128 | 68 | 60 |
| Dog | 28 | 46 | 25 | 102 | 75 | 27 |
| Pony | 171 | 30 | 24 | 97 | 74 | 23 |
| Horse | 460 | 44 | 45 | 85 | 63 | 22 |

where PaCO2 is arterial PCO2, PAO2 is calculated mean alveolar PO2, PcO2 is integrated pulmonary capillary PO2 during the blood's transit of the lung, and $\Delta$PO2 is the integrated difference between PAO2 and PcO2. Two factors contribute to create the increased $\Delta$PO2 in the smaller species: 1) lower PaCO2 raises the PO2 in the alveoli, and 2) respiratory alkalosis amplifies the Bohr shift as the blood is oxygenated in the lung causing it to maintain a lower PcO2. Supported by NSF grant PCM-83-17800.

37.10

HEART MITOCHONDRIA AND $\dot{V}O_2MAX$: ENDURANCE TRAINING EFFECTS IN RAT AND IGUANA. K.E. Conley*, K.A. Christian*, H. Hoppeler*, E.R. Weibel*, and C.R. Taylor. Univ. of Berne, CH-3012, Switzerland, Univ. of Puerto Rico, Rio Piedras PR 00931, and C.F.S., Harvard Univ., Bedford MA 01730.

Adaptation of heart mitochondrial volume (Vmt) to maximum $O_2$ delivery need ($\dot{V}O_2max$) was examined after a 5 day/week endurance running program in rats (Sprague-Dawley, 25 min/day for 6 weeks) and Cuban land iguanas (Cyclura nubila, 15 min per day for 8 weeks). Heart Vmt increased in direct proportion to $\dot{V}O_2max$ following training and a close linear correlation related Vmt to $\dot{V}O_2max$ in both species. Underlying the increase in heart Vmt in rats was an increased heart mass at a constant mitochondrial volume density (Vv), as is typical for adaptation of mammalian myocardium to endurance training. In contrast, the opposite occurred in the iguana: heart Vmt was unchanged but Vv increased, as is typical for endurance trained skeletal muscle. Thus, both rat and iguana showed an increase in heart Vmt in direct proportion to $\dot{V}O_2max$ following endurance training; however, the structural changes underlying this increase in Vmt in the iguana were distinct from the adaptive changes typical of the mammalian myocardium. (Sponsored by grants NIH 1 F32 HL07059-01, 2S06 RR08102-13, and Swiss NSF 88.038.0.82.)

37.11

EPINEPHRINE, ORGANIC MOLECULES AND VENTRICULAR FIBRILLATION IN DOGS. Nathan Hiatt and Jonathan Hiatt.* Cedars-Sinai Medical Center, Los Angeles, CA 90048. UCLA Medical Center, Los Angeles, CA 90024.

In a dog with a normal ECG (regular sinus rhythm) the response to an intravenous (IV) injection of 25 ug epinephrine/kg is about 20 seconds of no change, followed by approximately 15 seconds of sinus or ventricular bradycardia-then some 2 minutes of ventricular tachycardia that gradually subsides; regular sinus rhythm is restored 4-5 minutes after the injection. The response to epinephrine is unchanged by an IV injection, 3 minutes before, of either 4 ml or 0.2% phenol or 1.6% glycerol. However, if the two are given simultaneously, the subsequent injection of epinephrine produces ventricular fibrillation in 18 seconds. In rat myocardium there are 18 fentomoles B receptor/mg protein (SCarpace, Fed. Proc. 45:51, 1986). In the phenol-glycerol mixture there are 5.4 X $10^{20}$ molecules (0.0008/78 X 6.02 X $10^{23}$ phenol, plus 5.4 X $20^{20}$ glycerol) - probably more than enough to alter the B receptor response to epinephrine. Since the normal plasma concentration of epinephrine (molecular weight 183) is about 100 pg/ml (Dimsdale, Hartley, Ruskin, Greenblatt, LaBrie: Am. J. Cardiol. 54:182, 1984) - 3.3 X $10^{11}$ molecules - a concentration that may increase many fold with physical or mental stress, it is possible that a burst of endogenous epinephrine abetted by a large number of harmless molecules, may produce ventricular fibrillation and sudden death.

37.12

**ENERGETIC AND THERMOREGULATORY CONSEQUENCES OF SOCIAL BEHAVIORS BY TOWNSEND VOLES.** **R.V. Andrews*, D. Phillips, and D. Makihara.** Physiology Dept., Creighton Univ., Omaha, Nebraska 68178 and Zoology Dept., U.B.C., Vancouver, B.C.

**Novel behavioral encounters between strange voles resulted in core temperature increases that were proportional to behavioral reaction intensities; low intensity reactions such as avoidance behaviors were associated with 0.8°C rises in core temperatures, while fighting and chasing behaviors produced 1.6-2.0°C increments of body temperature. When novel encounters were staged in metabolism chambers, increases in metabolic rate and thermal conductance accompanied the behaviorally-induced hyperthermia. Protracted cohabitation of the chambers resulted in increased social tolerance, so that within 2 days, animals were huddling and did not show agonistic displays. Huddling behaviors resulted in 16% reductions in the animals' metabolic rates and thermal conductances in the face of higher resting core temperatures. These changes are consistent with changes in autonomic tone which accompany changes in behavioral tolerance between voles.**

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38.1

COMPARISON OF INTRATHORACIC TEMPERATURES DURING EXERCISE AND RECOVERY IN NORMAL AND ASTHMATIC SUBJECTS. I.A.Gilbert*, K.A.Lenner*, J.M.Fouke, A.J.Coreno and E.R.McFadden, Jr. Case Western Reserve University, Cleveland, Ohio 44106.

We have suggested that the bronchial circulation is thermally sensitive and that cooling produces vasoconstriction followed by a reactive hyperemia which, if sufficiently severe, could produce airway obstruction. If this sequence occurs, the temperature (T) within the airways should fall with exercise (Ex) and then abruptly rise with its cessation. To test this possibility, we recorded airstream T at multiple points within the tracheobronchial tree in 5 normal (N) and 4 asthmatic (A) subjects during and after cycle ergometry while breathing frigid air. In both groups airstream T fell progressively as ventilation ($\dot{V}_E$) increased and there were no significant differences between populations during Ex for either variable (T end-Ex mid-trachea N=26.6±0.5, A=26.4±0.8°C; Right lower lobe N=29.3±0.6, A=28.6±0.8°C; $\dot{V}_E$ N=49±4, A=42±5 L/min). During recovery, however, in the asthmatics, T rose rapidly and reached resting levels within 5 sec while the normals required 30 to 45 sec to achieve the same end point. (ΔT Ex to recovery mid-trachea @ 15 sec N= 3.7±0.6, A=6.9±1.1°C.) It appears that asthmatics condition inspired air in the same fashion as normal subjects during periods of thermal stress. However, when hyperpnea ceases in asthmatics, airstream T rapidly rises. Since the only source of the increase in heat is the blood supply, these findings are compatible with a rebound hyperemia.

38.2

CLOSING PRESSURES, DILATING FORCES, AND SITES OF POTENTIAL UPPER AIRWAY CLOSURE. K.P. Strohl, A.D. Wolin*, E. van Lunteren, J.M. Fouke. Case Western Reserve University, Cleveland, OH 44106

To determine how muscles contribute to upper airway stability, we monitored, in six anesthetized, ventilated, apneic dogs, the closing pressure for the nasopharyngeal and oropharyngeal passages before and after bilateral electrical stimulation of the sternohyoid, sternothyroid, ceratohyoid, genioglossus, and geniohyoid muscles. Before stimulation, the pressure required to close the naso- and oro-pharyngeal passages was -10.1 +/- 2.3 and -3.5 +/- 1.5 $cmH_2O$, respectively. Low levels of stimulation to any muscle pair resulted in greater negative closing pressures for the nasopharyngeal passage; however, the oropharyngeal passage closed as readily with as without stimulation. Using pressure in the sealed upper airway as an index of muscle force, we found that the production of a dilating force correlated with the change in nasopharyngeal closing pressure. We conclude that, in this preparation, muscles of the anterior and lateral pharyngeal wall prevent nasopharyngeal rather than oropharyngeal closure and that these muscles reduce airway collapsibility through airway dilation. HL 01067 and 29726

38.3

VAGALLY INDUCED INCREASE IN PULMONARY RESISTANCE IS MEDIATED BY M1 RECEPTORS. K.C. Beck, J. Vettermann*, N.A. Flavahan*, and K. Rehder. Mayo Clinic and Foundation, Rochester, MN 55905

Two muscarinic receptors (M1 and M2) have been identified; their physiologic role in vagal control of pulmonary resistance is unclear. The effects of pirenzepine (PZ, M1-blocker), gallamine (GAL, M2-blocker) and atropine (AT, M1- and M2-blocker) on the increase in pulmonary resistance ($R_L$) and reduction in heart rate (HR) from bilateral cervical vagal stimulation (25 V, 3 ms, 15 Hz) were tested in 18 anesthetized (15 mg/kg chloralose, 150 mg/kg urethane), paralyzed (0.04 mg/min Vecuronium) dogs. Mean (± SE, n = 6) doses (mg/kg) resulting in 50% inhibition of the initial HR- and $R_L$-responses to vagal stimulation are listed for 3 groups of 6 dogs each:

| | PZ | GAL | AT |
|---|---|---|---|
| HR | 3.81 ± 0.25 | 2.23 ± 0.62 | 0.067 ± 0.016 |
| $R_L$ | 0.084 ± 0.009 | > 9.6 | 0.0055 ± 0.0016 |

For PZ, this dose was about 50 times larger for the HR- than for the $R_L$-response. GAL inhibited the HR- but not the $R_L$-response. The nonselective M1- and M2-blocker, AT, inhibited both the $R_L$- and HR-responses. These data suggest that the bronchoconstrictive effect of vagal stimulation is predominantly by M1 receptors. Supported by HL 30937 and HL 21584.

38.4

CHANGES IN BRONCHIAL REACTIVITY TO METHACHOLINE IN SENSITIZED RATS REPEATEDLY EXPOSED TO INHALED ANTIGEN. S. Bellofiore* and J.G. Martin* (SPON: J. Milic-Emili). Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada H3A 2B4

Airway responses to inhaled methacholine (MCh) were measured before and after repeated antigen exposures in 10 male inbred BN rats (130-205 g) actively sensitized to ovalbumin (OA). On each study day rats were anesthetized with xylazine (7 mg/kg) and pentobarbital (30 mg/kg) and intubated with a polyethylene tube (PE240). Airway responses were quantitated using pulmonary resistance ($R_L$). Six challenges with OA were performed at 5 day intervals beginning 19 days after sensitization. OA (5% W/V in saline) was inhaled for 1, 2, 5, 10 or until $R_L$ increased by 50%. MCh challenges were performed before and 14 days after sensitization, 2 days after the third OA exposure and 2, 7, 12, 17 days after the sixth OA challenge. Aerosols of doubling concentrations of MCh (from 1 to 16 mg/ml) were inhaled and the concentration required to increase $R_L$ to 200% of the control value ($ED_{200}R_L$) was calculated. Seven rats responded to OA with an increase in $R_L$ greater than 50%. All 7 decreased their $ED_{200}R_L$ from a control value of 3.97 (log mean) to 1.84 mg/ml ($p < 0.05$) after the 3rd challenge and to 1.49 mg/ml ($p < 0.005$) after the 6th challenge with OA. $ED_{200}R_L$ recovered gradually but at 12 days after the end of the exposure period it was still significantly reduced. In the 3 unreactive rats $ED_{200}R_L$ did not change after exposure to OA. We conclude that repeated exposures to inhaled OA cause an increase in bronchial reactivity to MCh in sensitized rats that develop immediate reactions to the inhaled antigen. (Supported by the Medical Research Council of Canada)

38.5

ATRIAL RECEPTORS (AR) AND REFLEX TRACHEAL TONE (TT). K.K. Teo*, G.C.W. Man and C.T. Kappagoda, Dept. of Medicine and SMRI, Univ of Alberta, Edmonton, Alberta, Canada T6G 2R7.

It has been shown previously that partial obstruction of the mitral valve (MVO) causes a reflex increase in TT (Physiologist, 28:303,1985). In the present study the role of AR in this reflex was examined. The investigation was done in 7 dogs anesthetized with α-chloralose and artificially ventilated. AR were stimulated by the following protocols (1) partial MVO, (2) partial obstruction of the tricuspid valve, (3) stretching the right atrial-superior vena cava junction internally, (4) stretching the left pulmonary vein-atrial junctions externally. The hemodynamic changes were as follows:

| Protocol | n | HR (b/m) | | Atrial Pr.(mm Hg) | |
|---|---|---|---|---|---|
| | | Control | Stim | Control | Stim |
| 1 | 10 | 143±9 | 185±21 | 6.8±0.4 | 16.3±0.3 (left) |
| 2 | 12 | 171±8 | 194±5 | 5.1±0.3 | 7.5±0.4 (right) |
| 3 | 5 | 157±6 | 175±6 | 4.6±0.5 | 4.4±0.3 (right) |
| 4 | 10 | 131±6 | 158±8 | 7.1±0.3 | 7.6±0.5 (left) |

An increase in TT (+6.0±0.9 g from 91.2±4.4 g $p<0.05$) was seen only in protocol 1, the only procedure associated with an increase in LAP. It is suggested that stimulation of AR alone does not cause a reflex increase in TT and that the reflex increase in TT following MVO is due to activation of receptors in the lung.

38.6

GRADED CHANGES IN TOTAL LUNG RESISTANCE EVOKED BY THE CAROTID BAROREFLEX IN DOGS. H.D. Schultz, H.M. Coleridge and J.C.G. Coleridge. Cardiovascular Research Institute, UCSF, San Francisco, CA 94143.

Because we have shown previously that the carotid baroreflex evokes graded changes in tracheal smooth muscle tone, we sought to determine whether baroreceptors also affect the distal airways. In chloralose anesthetized dogs breathing spontaneously, we distended the vascularly isolated carotid sinuses with a pulsatile pressure and measured total lung resistance breath by breath, using a Buxco pulmonary mechanics analyzer. Increasing mean carotid sinus pressure in steps between 100 and 200 mm Hg decreased breathing rate, tidal volume, tracheal smooth muscle tension, and lung resistance; decreasing sinus pressure between 100 and 50 mm Hg had the opposite effects. Changing carotid sinus pressure in open chest, artificially ventilated dogs had similar effects on lung resistance. All reflex effects were abolished by cutting or cooling (0°C) the carotid sinus nerves. Airway responses were abolished by atropine. Changes in total lung resistance evoked by the carotid baroreflex were of comparable magnitude to those triggered by laryngeal receptors and pulmonary C-fibers. Our results indicate that carotid baroreceptor input influences bronchomotor tone in both the upper and lower airways. (Supported by N.I.H. Grants HL-33797, HL-25847 and HL-24136).

38.7

RAPID POTASSIUM SHIFT IN EXERCISING ASTHMATIC PATIENTS. F. Haas, N. Levin, K. Axen, and H. Pineda. New York University School of Medicine, New York, 10016.

Plasma potassium ($K^+_p$) rises during exercise and returns to baseline within 10 minutes after exercise stops. Adrenoceptors appear to modulate this response. Altered adrenoceptor function has been postulated in asthma. We reasoned that if this were the case post-exercise $K^+_p$ would remain elevated in asthma patients. $K^+_p$ and $FEV_1$ were measured in 9 healthy subjects (C), and in 13 asthmatic subjects (A) before treadmill exercise, at peak exercise, and 10 minutes after exercise. Both groups exercised to 95% of their predicted maximum heart rate. $K^+_p$ before exercise were similar (4.1 ± 0.1 and 4.1 ± 0.1 mmol/L, C and A respectively, m ± SE), at peak exercise, Kp rose to 4.7±0.1 in C, and 4.9 ±0.1 in A ($P<0.001$). $K^+_p$, in C after exercise, had returned to baseline (4.2 ±0.2). Kp in A, however, remained elevated (4.7±0.2, $P<0.01$). After exercise, $FEV_1$ in C remained unchanged but decreased in A to 74 ±5% of baseline ($P<0.001$). No correlation between $K^+$ response and drop in $FEV_1$ were observed, suggesting that an association--but not a causal relationship--exists. This data supports the hypothesis that asthmatics have altered adrenoceptor function. (Supported by NIH grant HL/28537)

38.8

**CHANGING PATTERN OF BREATHING STRATEGY IN THE FIRST YEAR OF LIFE.** **Andrew A. Colin*, Ann R. Stark*, Jere Mead, Gary Glass*, Mary Ellen B. Wohl. Harvard Medical School. Boston, MA 02115.**

**In contrast to adults, newborn infants actively maintain end-expiratory volume (EEV) above relaxation volume. This strategy is partly accomplished by inspiratory interruption of relaxed expiration. To characterize the pattern of transition from infant to adult strategy, we used Respiratory Inductance Plethysmography (RIP) to study 24 children ages 1 mo-8 yrs, during quiet breathing in natural sleep at home. The RIP rib cage and abdominal signals were summed to represent volume, digitized and differentiated to represent flow. Breathing strategy was assessed from the configuration of the expiratory flow volume curve in 50 randomly selected breaths/child. In 5 children simultaneous pneumotachographic flow measurements confirmed the validity of the RIP method. The number of children in each age group using relaxed (>80% relaxed breaths), intermediate (50-65% relaxed breaths), interrupted (>90% interrupted breaths) strategies are given below:**

| Age | Relaxed | Intermediate | Interrupted |
|---|---|---|---|
| 1-6 mo | 3 | 2 | 5 |
| 7-12 mo | 3 | 3 | 0 |
| >13 mo | 8 | 0 | 0 |

**We conclude that a transition from the predominantly interrupted infant strategy to relaxed expiration occurs in the second half of the first year of life. By the second year children appear to have a mechanically determined EEV.** **(Supported by NHLBI SCOR grant HL-34616)**

38.9

RELATIONSHIPS AMONG INDICES OF DIAPHRAGMATIC FATIGUE DURING SHOCK

S. Hussain*, J. Marcotte*, H. Burnet*, P. Collett* and Ch. Roussos. McGill University, Montreal, Quebec H3A 2B4

In the diaphragm of 6 dogs we studied the relationships among the changes in the centroid frequency [Cf], High/Low ratio [H/L], time constant of relaxation [$\tau$], the ratio of peak spontaneous EMG [$E_{di}$] and pressure [$P_{di}$] and $P_{di}$ during phrenic nerve stimulation at 20, 50, 100 Hz ($P_{di}$ 20, 50, 100). All parameters were measured during control and every 15 minutes during hypotension (arterial pressure [$P_{art}$] = 40-50 mmHg) which was maintained until $P_{di}$ 100 fell by 25% of control (fatigue time [FT]). $P_{di}$ 20, 50, 100 declined to 85%, 73% & 76% of control [C] only at 100% FT (100 min). $\tau$ was also prolonged only at 100% FT, whereas Cf and H/L ratio declined progressively to 70% and 31% of C at 100% FT respectively. At 40% FT, $P_{di}$ and $E_{di}$ increased to 148% and 184% of C but then declined to 121% and 151% at 100% FT respectively. $E_{di}/P_{di}$ increased to 130% of C at 60% FT with no change thereafter. During recovery ($P_{art}$ 90 mmHg), $P_{di}$ 20, 50, 100 recovered slowly (89%, 89%, 104% of C at 60 minutes) whereas Cf, H/L and $E_{di}/P_{di}$ recovered to control within 15-30 min. We conclude that during hypotension: 1) all tests showed that diaphragmatic fatigue occured in this model, 2) the changes in Cf, H/L and $E_{di}/P_{di}$ preceed diaphragmatic fatigue defined by pressure output, 3) the magnitude of changes in pressure were less than those of the EMG power indices but similar to those of the $E_{di}/P_{di}$.

38.10

EFFECT OF MINIMUM TRANSPULMONARY LOOP PRESSURE ON PRESSURE-VOLUME HYSTERESIS IN EXCISED RAT LUNGS. W. Cheng*, D. G. Frazer and D. DeLong*. Dept. of Physiol., West Va. Univ., DRDS, NIOSH, Morgantown, WV 26505

Excised lungs from Long Evans Hooded male rats were inflated-deflated in an air-filled plethysmograph. Lungs were initially inflated from the degassed state to 30 $cmH_2O$ then deflated to -5 cm $H_2O$. On the second cycle lungs were inflated with a sinusoidal volume perturbation (5-10 cycles/min) superimposed on a slow constant inflation rate. The resulting inflation pressure-volume ($P_L$-$V_L$) curve consisted of a series of $P_L$-$V_L$ loops whose maximum (Pmax) and minimum (Pmin) transpulmonary pressures, tidal volume ($V_T$) and hysteresis area (A) were recorded. When $A/V_T$ was plotted vs $\Delta P$ (Pmax-Pmin) for each $P_L$-$V_L$ loop an approximately linear relationship ($A = K \cdot V_T \cdot \Delta P$) was found for those loops whose end-expiratory volume was above 50% TLC. These results are similar to those previously described by Hildebrandt et al. (J. Appl. Physiol. 31:423, 1971). When end-expiratory volume was reduced to lower values, so that $P_L min < 4$ cm $H_2O$, a second relationship was found in which $A/V_T$ assumed a greater value for a given value of $\Delta P$. The difference between the first and second curves increased as a function of $\Delta P$. Based on previous findings, it is believed that the $A/V_T$ difference between curve 1 and 2 at the same $\Delta P$ reflects the changing contribution of the recruitment-decruitment process to loop hysteresis.

38.11

HYPERCAPNIA HAS FREQUENCY DEPENDENT EFFECTS ON RESISTANCE IN THE CAT. Peter D. Sly*, J.H.T. Bates*, T. Kochi*, S. Okubo*, and J. Milic-Emili. Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada H3A 2B4

The published effects of inhaling different concentrations of $CO_2$ on respiratory mechanics are controversial. Hypercapnia has been reported to increase, have no effect on, and decrease resistance. This confusion may be due to the different methods used for measuring resistance, which is known to be frequency dependent. In this study the effect of hypercapnia on resistance was investigated in 6 anesthetized, paralyzed, tracheostomized cats ventilated by constant flow inflation. Zero frequency resistance (Rmax), infinite frequency resistance (Rmin) and static elastance (Est) were calculated from end inspiratory occlusions, for the respiratory system, lung and chest wall. Alveolar ventilation was manipulated by the addition of dead space to achieve a range of $PaCO_2$ values from 29.3 to 87.3 mmHg. Ventilatory parameters were kept constant and hypoxia prevented ($F_{IO_2}$ = 0.35). With hypercapnia, Rmax of the lung increased ($p < 0.01$) but Rmin did not. There were no changes in chest wall resistance or in the static elastic properties of the lung or chest wall. These results suggest that hypercapnia increases resistance in the lung periphery but not in the conducting airways. Those studies which previously reported an increased resistance used methods measuring the low end of the "resistance-frequency" spectrum, similar to Rmax while those reporting no change used techniques measuring the high end of the spectrum similar to Rmin. Thus the apparent controversies appear to be due to methodological differences.

38.12

THE MEASUREMENT OF RESPIRATORY RESISTANCE BY FLOW INTERRUPTION IS AFFECTED BY NON-INSTANTANEOUS OCCLUSION OF THE AIRWAY OPENING. J.H.T. Bates*, I.W. Hunter*, P.D. Sly*, S. Okubo*, S. Filiatrault*, and J. Milic-Emili. Meakins-Christie Laboratories and Biomedical Engineering Unit, McGill University, Montreal, Que., Canada H3A 2B4

The resistance of the respiratory system to flow may in principle be measured by the flow interruption technique, in which the flow of gas at the mouth of a subject is suddenly interrupted while the pressure just distal to the point of interruption is recorded. There is a rapid change in pressure immediately upon interruption, approximating the resistive pressure drop across the pulmonary airways. This is followed by a further slow change in pressure reflecting stress relaxation in the respiratory system and gas redistribution between different regions of the lung. The diagnostic potential of the post-occlusion pressure signal is dependent on the airway opening being occluded effectively instantaneously. We have designed and built an occlusion valve for performing rapid airway occlusions. We are able to measure the closing characteristics of the valve precisely, and have shown that its finite closure time of 12 ms causes the initial rapid drop in pressure to be underestimated by about 7%, while the subsequent pressure drop is almost unaffected. A simple numerical correction scheme allows us to estimate this pressure drop correctly to within one or two percent. By collecting flow and pressure data directly with a computer and extrapolating the signals to the point in time when the valve is half closed we are able to obtain on-line values of interrupter resistance.

38.13

EFFECT OF CHANGES IN INSPIRATORY VOLUME AND POSTURE ON INTRATHORACIC AND INTRAGASTRIC PRESSURES DURING GRADED VALSALVA MANEUVERS. CJM Porth, JK Pikna*, University of Wisconsin-Milwaukee, Milwaukee, WI 53211

The overall objective of this study was to determine the effects of posture (standing, seated and supine) and inspiratory volume (40%, 70% and 100% vital capacity [VC]) on heart rate (HR), airway pressure (AWP), esophageal P (EP), and gastric P (GP) during 15 sec graded (10, 25 and 40 mm Hg) Valsalva maneuvers (VM) in 9 healthy male subjects, ages 20 to 35 years.

Results of this study showed parallel changes in EP and GP during each of the graded VMs. There were greater differences between AWP and EP at higher lung volumes (70% and 100% VC) as compared to lower lung volumes (40% VC) during graded VM performed in all 3 positions. The increase in GP was greatest when the VM was performed in the standing position. Phase II and III HR increases were greatest when the VM was performed at low lung volumes.

The greater difference between AWP and EP during higher lung volumes may reflect changes in lung compliance. The greater increase in GP during the 40 mm Hg VM performed in the standing position, the effects of gravity on intra-abdominal contents.

(Supported by a grant from the Am Lung Assoc of Wis.)

38.14

THE EFFECT OF INSPIRATORY RESISTIVE LOADING ON THE OXYGEN COST OF BREATHING DURING HEAD-OUT IMMERSION. E.J. McCarthy*, J.R. Clarke, P. Karnik*, D.L. Shearer*, E.T. Flynn*. Naval Medical Research Institute, Bethesda, MD 20814-5055.

The effect of head-out water immersion (HOI) on the cost of breathing and ventilatory response to external resistive loads was examined in 4 Navy divers. Four resistors (orifice diameter 2.25-1.5 mm; R1-R4) were applied to the inspiratory limb of an open-circuit breathing system. Subjects were exposed for 10 min to each of 5 resistance conditions; RO (unloaded)-R4 in order of increasing resistance. Each subject performed duplicate runs during HOI and in the dry. Expired gases were collected, and measurements of oxygen consumption ($\dot{V}O2$), minute inspiratory ventilation ($\dot{V}I$), arterial hemoglobin-oxygen saturation (SaO2), end tidal CO2 (ETCO2), and average peak mouth pressure (Pm), were made during the last 2 min of each 10 min exposure. Peak inspiratory mouth pressures ranged from 24 to 55% of the maximum inspiratory pressure at FRC. ETCO2 increased approximately 30% both in the dry and during HOI. SAO2 decreased from 95.3±.5%(RO)(mean ± SEM) to 91.8±1.0% (R4) during immersion and 95.5±.5% (RO) to 93.6±.6% (R4) in the dry ($p<0.05$). The oxygen cost of breathing per unit of inspiratory ventilation($\Delta\dot{V}O2/\dot{V}I$) increased in both HOI (5.4±3.4 mlO2/L, R1; 23.1±4.1, R4) and in the dry (7.67±3.71, R1; 24.0±3.1, R4) ($p<0.05$). There was no significant difference in either $\dot{V}O2/\dot{V}I$ or other measured variables between HOI and the dry exposures.

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38.15

THE EFFECT OF AMBIENT PRESSUE AND GAS ON SOUND SPEED IN THE LUNG. David A Rice*, Stanley J. Whidden and Janet C. Rice*. Department of Biomedical Engineering, Tulane University, New Orleans, LA 70118.

We measured the time it takes sound to travel from the trachea to the back over the right lower lung lobe. Delay time is the time difference between the leading edge of short, 251 Hz pulses injected through a mouth cannula in a normal volunteer. The delay times are shown in ms (S.D.):

| gas | pressure 1 | 2.1 | 4 ATA |
|---|---|---|---|
| air | 3.50(0.11) | 3.20(0.25) | 2.61(0.14) |
| He-20%$O_2$ | 2.56(0.34) | 2.32(0.17) | 2.25(0.09) |

$HeO_2$ caused shorter delays than air ($p<0.001$); higher pressures decreased delays ($p<0.001$); pressure had a greater effect with air then with $HeO_2$ ($p<0.05$). Previous work shows that sound speed in gas is independent of pressure (P), but sound speed in pulmonary parenchyma is independent of gas composition and is proportional to $P^{\frac{1}{2}}$. Assuming that sound propagates in the airways at free field speeds then transfers to the parenchyma, the time delay should be dependent upon the sum of two terms: free field sound speed in the gas and a $P^{-\frac{1}{2}}$ term. A statistical model using these fits well. Including a pressure-gas interaction term significantly improves the fit ($R=0.91, p<0.05$). This suggests that the place along the airways where the sound transfers to the parenchyma moves with changes in gas and pressure.

Supported by NHLBI grant HL30359 and the JESM Baromedical Research Institute.

38.16

**BROADBAND ACOUSTICAL IMPEDANCE OF EXCISED RAT LUNGS AT TRANSPULMONARY PRESSURES BETWEEN -5 CM AND 30 CM $H_2O$.** **Krishnamurthy Jayaraman* and David Frazer**. DRDS, NIOSH, Morgantown, WV 26505

**Acoustical reflections from excised rat lungs have been measured over a frequency range of 100 to 5000 Hz during both inflation and deflation between transpulmonary pressures ($P_L$) of -5 cm and 30 cm $H_2O$. This was achieved with two closely spaced B&K microphones in an impedance tube coupled at one end to a speaker driven by white noise and at the other end to the excised lung. The connector to the lung was carefully characterized by a 4-pole transmission matrix with open, clamped and characteristic terminations. The transfer function between the two microphone outputs was used to determine first an overall reflection coefficient function; next the connector transmission matrix was used to calculate the acoustical impedance of the lung over the frequency range. The results show different systematic trends with $P_L$ in lung impedance over different frequency bands. Peak impedance magnitudes between 1 and 3 kHz display a minimum as $P_L$ is decreased from 30 cm to -5 cm; however peak impedance magnitudes between 3 and 5 kHz increase monotonically as $P_L$ is decreased from 30 cm to -5 cm. The higher frequency band data are in accord with area changes; the other frequency band data seem to be affected by the stiffening of airway walls at higher values of $P_L$. On inflation, although similar trends were observed, the peak impedance magnitudes (over the lower frequency range) attained a minimum at higher values of $P_L$.**

38.17

**THE DETERMINATION OF THE RESONANT FREQUENCY OF THE RESPIRATORY SYSTEM ABOVE 50 HZ.** **S. S. Kraman**. **VA Medical Center, Lexington, KY and Univ. of Kentucky, Lexington, KY 40536.**

**The natural mechanical resonant frequencies of the respiratory system are of interest to physiologists because of their relevance to respiratory mechanics and to the phenomenon of high frequency ventilation. The present study was designed to evaluate the lung for resonant frequencies between 50 and 1200 Hz. Five healthy subjects were studied. Sound was introduced through an acoustic driver and mouthpiece and was picked up from the neck overlying the trachea and four locations over the posterior chest wall (upper and lower chest, bilaterally). Resonant frequencies were determined by calculation of the transfer function between signals detected at the tracheal and each of the four chest locations. The input signal was the spectrum of harmonics generated by a 25 Hz square wave. The transfer functions were measured and compared with the subjects breathing air and again after breathing a mixture of 80% helium in 20% oxygen (He-O2). Results: All transfer function plots showed one or more peaks between <50 and 167 Hz with variable roll-off of transmission up to 400 Hz. Virtually no transmission was detected above this frequency. For the group, the mean frequency of the major amplitude peak was 81 Hz (range: 50 to 167 Hz) at the upper chest wall locations and 64 Hz (range: <50 to 75 Hz) at the lower. With He-O2, the transfer function plots were similar or nearly identical to those with air. Conclusion: The human adult respiratory system appears to contain acoustic resonances at one or more discrete frequencies up to approximately 160 Hz. In these subjects transmission of sound was very poor above 400 Hz up to the maximum studied frequency of 1200 Hz.**

38.18

NON-INVASIVE ESTIMATION OF INTRA-AIRWAY HEAT TRANSFERS. Julian Solway, Daniel Ray*, Gregory Crawford*, Mary Strek* and Edward Ingenito.* Univ. of Chicago, Chicago, IL 60637.

The single breath temperature washout (SBTW) curve is generated by plotting exhaled gas temperature against exhaled volume (V) following a single inhalation of frigid air. We have developed an analysis of the initial (airways) portion of the SBTW which allows estimation of gas-wall heat transfer coefficient (h[V]) as a function of distance into the lung (V). We assume that the temperature of a 5 ml aliquot of inhaled gas decays exponentially toward airway wall temperature according to local conditions within the airways through which the gas aliquot passes. The local exponential decay rate (K[V]) equals $4 \cdot h[V] / \rho \cdot C_p \cdot d(V)$, where $\rho$ is gas density, $C_p$ is gas specific heat, and d(V) is local airway diameter. Iterative application of this analysis allows calculation of K(V) for successive 5 ml aliquots, so that K(V) is estimated throughout the airways. To test the validity of this approach, we obtained SBTW curves in a straight copper tube (1.27 cm i.d.) and compared h(V) values in a 50 ml segment to those determined during steady unidirectional flow. A close correlation between SBTW and steady flow h[V] values was found over a wide range of flows (0.5-2.4 L/sec). These results support the validity of heat transfer coefficients obtained by analysis of the SBTW curve. Application of this approach in human subjects should allow non-invasive estimation of intrapulmonary heat transfers.

Supp. by HL34702 and the Parker B. Francis Foundation.

38.19

NON-INVASIVE DETERMINATION OF INTRAPULMONARY HEAT EXCHANGE. Daniel Ray*, Gregory Crawford†, Mary Strek†, Edward Ingenito†, and Julian Solway. Univ. of Chicago, Chicago, IL 60637.

The single breath temperature washout (SBTW) curve is a plot of exhaled gas temperature versus exhaled volume (V) following a single breath of frigid air (ARRD 132:853-857, 1985). In this plot, exhaled gas temperature rises within the first 300 ml of expirate (corresponding to the airways region) to an alveolar plateau value. We applied a recently developed analysis of the airways portion of the SBTW to determine local gas-wall heat transfer coefficients (h[V]) at several sites within the central airways of 5 normal subjects. Airways were preconditioned to uniform temperature by breathing 37°C humidified air for 5-10 min. Subjects then inhaled 1-2.5 L of frigid air (-10°C) at 0.5 or 2.5 L/sec, and, without breathhold, exhaled at the same rate to inscribe the SBTW. Our results indicate that: 1) the analysis employed is insensitive to the volume of frigid air inhaled; 2) a similar dependence of h[V] on flow rate was seen in all subjects; and 3) h[V] within the trachea increases approximately linearly with flow and falls 20-40% below values predicted for fully developed turbulent flow in a rigid pipe. We speculate that local gas-wall heat transfer coefficients measured in this way will allow non-invasive estimation of airway wall temperatures following a variety of airway preconditioning regimens. Supported by HL34702 and the Parker B. Francis Foundation.

38.20

PULMONARY RAPIDLY ADAPTING RECEPTORS REFLEXLY EVOKE TRACHEAL SUBMUCOSAL GLAND SECRETION IN DOGS. J. Yu*, H.D. Schultz, J. Goodman*, B. Davis, J.C.G. Coleridge and H.M. Coleridge. Cardiovascular Research Institute, UCSF, San Francisco, CA 94143.

We sought to determine whether stimulation of rapidly adapting receptors (RARs) evokes tracheal submucosal gland secretion. In 9 anesthetized, artificially ventilated, open chest dogs we measured the secretions from the gland ducts by counting the hillocks appearing in a 1.2 $cm^2$ field of tracheal epithelium coated with powdered tantalum. We stimulated RARs by deflating the lungs. Secretion rate increased from 4.1±0.5 to 7.0±1.2 hillocks/min (mean ± SE) when positive end expiratory pressure (PEEP= 4cm $H_2O$) was replaced by atmospheric pressure, and to 13.2±1.7 hillocks/min when PEEP was replaced by -4 cm $H_2O$. When PEEP was restored, lung compliance had decreased to 60% of control. The decrease in compliance also caused a significant increase in secretion rate. All secretory responses were prevented by cooling the vagus nerves to 6°C. Both deflation of the lungs and a decrease in lung compliance stimulate RARs. We conclude that stimulation of RARs evokes reflex secretion from tracheal submucosal glands. (Supported by N.I.H. Grants HL-24136, HL-25847 and HL-33797, and by the Cystic Fibrosis Foundation.)

38.21

EFFECT OF CAROTID BAROREFLEX AND CORONARY CHEMOREFLEX ON TRACHEAL SMOOTH MUSCLE AND SUBMUCOSAL GLANDS IN DOGS. B. Davis, H.D. Schultz, J. Goodman*, H.M. Coleridge and J.C.G. Coleridge. Cardiovascular Research Institute, U.C.S.F., San Francisco, CA 94143.

Stimulation of several afferent inputs (carotid chemoreceptors, laryngeal receptors and lung C-fibers) evokes reflex contraction of airway smooth muscle and increased secretion by tracheal submucosal glands. Because carotid baroreceptors and cardiac vagal chemosensitive C-fibers have been shown recently to affect airway smooth muscle tone we sought to determine whether they also influence submucosal gland secretion. In anesthetized dogs we measured submucosal gland secretion by counting the hillocks appearing in a 1.2 $cm^2$ field of tracheal epithelium coated with powdered tantalum. Increasing and decreasing pressure in the isolated carotid sinuses in 25 mmHg steps above and below a setpoint of 100 mmHg evoked reciprocal changes in tracheal tension, which were abolished by cutting or cooling the sinus nerves to 0°C, but had little effect on secretion. Similarly, stimulating cardiac vagal C-fibers by injecting 1 µg/kg capsaicin into the circumflex coronary artery evoked contraction of tracheal smooth muscle but had only minor effects on secretion. By contrast, laryngeal stimulation evoked tracheal contraction and copious secretion. Our results indicate that reflex contraction of airway smooth muscle is not invariably accompanied by reflex increase in submucosal gland secretion. (Supported by N.I.H. Grants HL-24136, HL-25847, and HL-33797, and by the Cystic Fibrosis Foundation.)

38.22

**PHASIC ALAE NASI AND GENIOGLOSSAL ACTIVITY IS MORE COMMON IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA (OSA) THAN NORMAL SUBJECTS.** **PM Suratt, RF McTier and SC Wilhoit. U of Virginia Medical School, Charlottesville, Virginia.**

**Although in patients with OSA electromyographic (EMG) activity of upper airway muscles decreases at apnea onset, EMG activity in normals has not been studied and compared to patients. Consequently, we measured alae nasi (an) and genioglossus (ge) EMGs with surface electrodes during sleep and wakefulness and EEGs, EOGs, flow, esophageal pressure and O2 sat during sleep in 8 patients with OSA and 6 normals. We also measured nasopharyngeal resistance during negative pressure (Rnp) in awake subjects. We then compared the percent of total sleep time in which phasic an and ge EMG activity was present in patients to normals. Each patient had more phasic EMG activity than did any normal during sleep ($p<0.05$):**

| | % PHASIC an | % PHASIC ge |
|---|---|---|
| OSA | 88±6 mean±SD | 70±20 |
| NORMALS | 19±21 | 9±10 |

**and also during wakefulness ($p<0.05$). EMG activity (moving time average) decreased in patients at apnea onset. Rnp was greater in patients than in normals ($p<0.05$). We conclude that normals are able to maintain a patent pharyngeal airway with less phasic activity than patients and that the increased phasic activity in patients occurs as a consequence of a narrow airway.**



41.1

**AGE-RELATED EFFECTS OF PHYSIOLOGICAL VASOACTIVE COMPOUNDS ON THE JEJUNAL CIRCULATION IN DEVELOPING SWINE.** **S. Diamant*, N.M. Buckley, and I.D. Frasier*. Albert Einstein College of Medicine, New York, NY 10461**

**Norepinephrine (NE), adenosine (A), and histamine (H) have been demonstrated to elicit responses in the mesenteric circulation of adult mammals. This study provides an initial inquiry into the time course of appearence and sensitivity of these responses in developing swine whose neural and autoregulatory controls of intestinal circulation undergo postnatal maturation. Swine, 12-14-day old (Gr I, n=5), and 18-29-day old (Gr II, n=5) were anesthetized with pentobarbital (25 mg/kg) and artificially ventilated. Aortic pressure and ECG were registered, and arterial blood gases, pH, body temperature, and hydration were maintained. The jejunum (Jej) was isolated, cut transversly at both ends, and the lumen fitted with cannulas. The ileal branch of the mesenteric artery was ligated, and phasic femoral and Jej arterial flows were recorded, and resistances (R) calculated. After systemic heparinization and atropinization, the Jej artery was perfused by pump with blood from carotid cannula, and perfusion pressure recorded. Mean maximal Jej R responses (± SE) to intraarterial injections of NE(0.0025-0.02 µg/kg), A(0.1-1 µg/kg), and H(0.01-0.1 µg/kg) were normalized to control values to indicate vasoconstriction (VC) or vasodilation (VD).**

| | NE | | A | | H | |
|---|---|---|---|---|---|---|
| | TD | VC** | TD | VD** | TD | VD** |
| Gr I | 0.01 | 1.06±0.02 | 0.25 | 0.88±0.05 | 0.05 | 0.94±0.03 |
| GrII | <0.003 | 1.68±0.16* | <0.10 | 0.71±0.06* | <0.01 | 0.64±0.03* |

*** $p\leq0.05$; ** at same doses; TD=Threshold dose**

**We conclude that intestinal vascular responses to NE are present at two weeks of life in swine, while responses to A and H are consistently present only after two weeks. The sensitivity to all compounds increases with age.**
**(Supported by NIH grant HL-21865)**

41.2

HISTAMINE (H) BLOCKADE INHIBITS INTESTINAL BLOOD FLOW AUTOREGULATION IN YOUNG SWINE. N.M.Buckley, S.Diamant* and I.D. Frasier*. Albert Einstein College of Medicine, New York, NY10461

Blood flow autoregulation during decreased arterial pressure in the small intestine has been demonstrated in fasting swine one month after birth (Buckley,et al,Biol.Neonate 49:229,1986). This capability was next tested during blockade of H type-1 receptors. Six 1-month-old swine were anesthetized with pentobarbital (30 mg/kg) and prepared for recordings of aortic pressure (P), and renal and superior mesenteric (intestinal) arterial flow (F) by noncannulating electromagnetic transducers. Renal and intestinal P/F relationships were determined simultaneously during step-decreases in P produced by clamping the supraceliac abdominal aorta. After obtaining control P/F data, a test dose of H (0.1 ug/kg) was injected into the superior mesenteric artery and an i.a. infusion of chlorpheniramine (0.1 mg/kg/min) was begun. Ten minutes later, a second set of P/F data was obtained and the test dose of H was repeated. Each P/F relationship was normalized to initial control P and F. Data were then grouped to determine the autoregulatory range of P over which F was maintained at ≥ 95% control. Before H blockade, this range extended to 88% control P for the intestinal circulation and 77% control P for the renal. During demonstrable H blockade in the intestinal circulation, its autoregulatory capability was lost but there was no change in renal F autoregulation. We conclude that H type-1 receptors are involved in intestinal F autoregulation during decreased P in young swine. (Supported by NIH grant HL-21865)

41.3

CHLORALOSE (Cl) ALTERS SOME BASELINE HEMODYNAMIC VALUES IN YOUNG LAMBS. R.F. Covert* and W.H. Drummond. Univ. of FL, Dept. of Pediatrics, Neonatology Div., Gainesville, FL 32610

Cl is a commonly used anesthetic in physiologic experimentation in animals. Little is known about its effects on baseline hemodynamics as compared to paired, unanesthetized control values. We evaluated the circulatory effects of Cl, 30 mg/kg IV or equal volume of vehicle (control, 4 cc/kg) on alternate days in our chronic lamb model. 22 lambs, age 4-27 days, had 26 paired studies in alternate order while spontaneously breathing room air. After baseline values were obtained in the conscious state, lambs were infused with Cl or vehicle and hemodynamic responses and ABG were evaluated at paired time points. Lambs had recovered from previous instrumentation for measuring systemic (SAP), pulmonary artery (PAP), and left atrial pressures (LAP). Cardiac output was measured with a main PA flow transducer. The ductus arteriosus was ligated. Systemic (SVR) and pulmonary vascular resistances (PVR) were calulated. Results were evaluated by ANOVA and paired t-test. All baseline circulatory and ABG values were similar. This dose of Cl induced anesthesia in 5-15 min. Cl lead to ↑ HR at each time point (all $p<.005$) and ↑ SAP by 20 min (79±3 to 73±2, $p<.03$). CO, PAP, LAP, SVR, PVR, resp rate and ABG were not different between groups; however, some individual animals variably experienced idiosyncratic ↑ PAP, ↑ PVR, and ↓ $pO_2$. Cl induced alterations in hemodynamics and oxygenation should be considered in experimental design.

Supported by The American Heart Association.

41.4

RESPONSES OF SMALL INTRAPULMONARY ARTERIES TO VASOACTIVE AGENTS IN FETAL AND NEONATAL LAMBS. J. A. Dunn, S. N. Sinha* and V. Lorch*. Univ. of Tennessee, Knoxville, TN 37916

We assessed responses to 125 mM KCl and log doses of norepinephrine (NE), epineprhine (EPI) and serotonin (5HT) in small intrapulmonary arteries of fetus and newborn lambs. Third (600-1200 μm id) and fourth (180-380 μm id) generation blood vessel segments were dissected from the lungs of neonatal lambs at 7 days preterm and 1, 7, and 21 days of age and mounted on a myograph to record isometric contractions. Responses to KCl in 3rd generation vessels remained similar, while responses of 4th generation vessels increased with age. Third generation vessel response was greater than 4th generation only at preterm. At all ages, 3rd generation vessels were more responsive to NE than 4th generation. No differences were detected between 3rd and 4th generation vessels to EPI at preterm and at 1 and 7 days, however, at 21 days 3rd were more responsive than 4th generation vessels. Responses to EPI and NE were never greater than 50% of the KCl response. No differences between 3rd and 4th generation vessels to 5HT were noted at any age, however, the 5HT response was typically 1.5 to 2 times greater than the KCl response. Response differences in the neonate over time between 3rd and 4th generation vessels may reflect variation in quanitity of smooth muscle, changes in receptor population, or biochemical maturation. We are currently analyzing smooth muscle quantity using electron microscopy to address these possibilities.

41.5

MATURATIONAL CHANGES IN ALPHA ADRENERGIC RECEPTOR TONE AND RESPONSIVITY IN NEONATAL COARCTATION. J.M. Luber, Jr.*, B.J. Buckley*, S. Diamant*, N. A. Kaplan*, B.J. Peterson*, N. Gootman* (SPUN: P.M. Gootman). Schneider Children's Hospital, New Hyde Park, NY 11042.

Periductal aortic coarctation (C) was produced via left thoracotomy in day old swine; a second group underwent sham (S) thoracotomy. The animals were studied at 2 wks (S1, n=8; C1 n=8) and 6 wks (S2 n=8; C2 n=8) under pentobarbital anesthesia. Brachial (B) and femoral (F) arterial (A) pressures (P), ECG, and renal (Ren), femoral (Fem), carotid (Car) and mesenteric (Mes) arterial flows were continuously recorded; resistances (R) were calculated and reported in peripheral resistance units. Baseline data (mean ± SE) are shown below; all pressures (mmHg) are systolic.

| | BP | FP | CarR | MesR | RenR | FemR |
|---|---|---|---|---|---|---|
| S1 | 129±5 | 129±5 | 3±0.5 | 1.0±0.3 | 3±0.8 | 3±0.4 |
| C1 | 141±6 | 108±5 | 2±0.3 | 1.0±0.2 | 4±0.7 | 6±1.0a |
| S2 | 130±5 | 130±5 | 1±0.1 | 0.5±0.2 | 1±0.1 | 2±0.2 |
| C2 | 175±7ab | 137±5a | 2±0.2a | 0.6±0.1 | 2±0.4a | 3±0.4a |

a = $p<0.05$ S vs C; b = $p<0.05$ C1 vs C2

P gradient was not different between C1 and C2. Phenylephrine (PE; 2, 5 and 10 mcg/kg) was administered as an iv bolus; mean ↑Δ ± SE to 5 mcg/kg PE are below.

| | CarR | RenR | FemR | Mean BP |
|---|---|---|---|---|
| S1 | 28.6±7.5 | 383±141 | 41.7±11.9 | 40.4±2.5 |
| C1 | 32.7±7.5 | 203± 39 | 5.2±6.2b | 33.1±3.2a |
| S2 | 98.2±32 | 541±163 | 26.5±10.5 | 44.1±3.7 |
| C2 | 30.7±8.5b | 490±158 | -2.3±2.9b | 31.3±3.3b |

a = $p<0.05$ ST vs C1; b = $p<0.05$ S2 vs C2

These results indicate that: (1) with C there are differences in alpha adrenergic receptor tone and responsivity among different vascular beds both above and below C which are related to the duration of C and (2) occurrence of systemic hypertension in C is age-dependent. Supported by American Heart Assoc., Nassau Chapter.

41.6

DISSIMILARITIES IN RESPONSE PATTERNS BETWEEN THE MESENTERIC AND RENAL VASCULATURES TO SUSTAINED HYPOVOLEMIA IN DEVELOPING SWINE. N. Gootman*, B.J. Buckley*, B.J. Peterson*, N. A. Kaplan* and P.M. Gootman. Schneider Children's Hospital of Long Island Jewish Medical Center, New Hyde Park, NY, 11042.

Following study of acute changes in cardiovascular (CV) function to sequential blood withdrawal (Buckley BJ et al., Am J Physiol, 247:R626, 1984), we investigated the compensatory CV responses to 20% reduction in estimated blood volume (by rapid withdrawal of arterial blood) sustained over 2 hrs in lightly anesthetized swine: 2 wk and 2 mo of age. Arterial blood gases and pH and body temperature were maintained. ECG, aortic pressure (AoP), heart rate (HR) and phasic superior mesenteric (Mes) and renal (Ren) arterial flows (F) were continuously recorded; mean AoP (AoP), mean F and vascular resistances (R) were calculated. Control experiments (n=16) were performed in different animals at each age (effects of the passage of time alone). Change (mean ↑Δ ±SE) from pre-hemorrhage level was calculated immediately (0 min) and every 15 min for 2 hrs and was analyzed by t-tests ($p<0.05$).

| | 2 Wk (n=5) | | | 2 Mo (n=9) | | |
|---|---|---|---|---|---|---|
| Time (min) | 0 | 30 | 120 | 0 | 30 | 120 |
| HR | 17±7* | NS | NS | 36±11 | 35±8 | 31±10 |
| AoP | -13±4 | NS | NS | -41±7 | -16±5 | -13±6 |
| MesF | -48±4 | -39±6 | -21±7 | -59±5 | -53±4 | -40±4 |
| RenF | -30±4 | -14±4 | NS | -52±9 | -28±4 | -26±5 |
| MesR | 70±15 | 63±22 | NS | NS | 102±32 | 61±18 |
| RenR | NS | NS | NS | NS | NS | NS |

*not significant due to variation in magnitude of responses

In controls, there were no significant changes in any CV parameter over 2 hr. Increases in HR and decreases in AoP were not sustained during hypovolemia in 2 wk as compared to the 2 mo olds. Mes vasculature was involved in compensatory response to hypovolemia, while the Ren vasculature only passively responded to the decrease in AoP, regardless of postnatal age. Supported by American Heart Assoc, Nassau Chapter and NIH HL-20864

41.7

CARDIAC OUTPUT (Q) FOLLOWING INDOMETHACIN TREATMENT FOR PATENT DUCTUS ARTERIOSUS (PDA). James W. Holcomb* and William R. Sexson. Emory University, Atlanta, Ga. 30306.

Patency of the ductus arteriosus commonly occurs in premature infants with respiratory distress. In these infants, cardiac output is generally elevated. Indomethacin (Indo) is used to non-surgically close the PDA. Impedance cardiography (IC) is a non invasive technique to assess Q. This study reports the use of IC to serially evaluate Q in premature infants with a PDA requiring Indo therapy.

Five infants were studied using a Minnesota 304B Impedance Cardiograph measuring the first derivative of transthorasic impedance, dZ/dt, to calculate Q. Infants studied were assessed clinically and felt to have a hemodynamically significant PDA that was not responding to treatment with fluid restriction or diuretic therapy. Treatment with Indo (0.1-0.2 mg/kg/dose q 12h for 3 doses) was administered parenterally. Q/kg using IC was measured prior to Indo, prior to the third dose, and 5-6 days after Indo was begun. None of the infants had clinical evidence of a PDA following therapy.

| Q/kg (ml/min/kg) | | | |
|---|---|---|---|
| Control | Pre-Indo | Prior to 3rd dose | 5-6 days after |
| 196 ± 70 | 280 ± 72 | 186 ± 44 | 219 ± 70 |

Indo therapy for PDA resulted in a marked decrease in Q/kg by 24 hours after it was begun.

41.8

REGIONAL MYOCARDIAL BLOOD FLOW DURING HEMORRHAGIC HYPOTENSION IN THE NEWBORN LAMB. Gary Pettett*, Errol Alden*, Stephen Golden*, Joseph Tuggle* and Timothy O'Neill. Dept of Pediatrics, USUHS, Bethesda, MD 20814

In this study we report the effects of hemorrhagic hypotension (HH) on regional myocardial blood flow (RMBF) 6 newborn lambs, 4-7 days of age, who were anesthetized and instrumented for radiolabeled microsphere flow studies. Blood flow was measured during a pre-hemorrhage control period and at mean arterial pressures (MAP) of 50, 40, and 30 mmHg. Arterial pressures was regulated by an external pressure-controlled reservoir attached to the animal via a hindlimb artery. Arterial $pCO_2$, $pO_2$ and pH were held constant by using intermittent mandatory ventilation and a continuous buffer infusion. Left ventricular work was estimated with pressure rate products (PRP). Although total coronary blood flow did not change, HH was associated with a significant reduction in LV endocardial blood flow (LVEF), LV $O_2$ delivery ($LVO_2D$) and cardiac output. In addition, the sequential reduction in MAP resulted in significantly lower PRP despite an increase in HR at both 40 and 30 mmHg. These results raise the possibility that the reduction in LVEF during HH occurred in response to a lower PRP. We tested this hypothesis by comparing $LVO_2D$ to PRP. There was no significant change in the $LVO_2D$:PRP ratio with progressive HH. We conclude that: A) the changes in RMBF during HH are the result of corresponding changes in ventricular workload and that B) the neonatal lamb is capable of regulating RMBF at MAP's as low as 30% of control levels.

42.1

STUDIES OF CALCIUM METABOLISM IN LACTASE DEFICIENCY IN MAN. Herta Spencer, Lois Kramer* and Clemontain Norris*. Metabolic Section, Veterans Administration Hospital, Hines, IL 60141

Metabolic balances of calcium and phosphorus were determined in three patients with lactase deficiency prior to and during the intake of 100 gm lactose per day, during the intake of milk containing 50 gm lactose and during the intake of equivalent amounts of lactose given during the same calcium intake as the gluconate. The intestinal absorption of calcium and the endogenous fecal calcium were determined with tracer doses of $^{47}Ca$. During the intake of 100 gm lactose, calcium balances were similar to those in control studies. The same was true during the intake of 50 gm lactose given as milk and during the intake of equivalent amounts of lactose and of calcium. The absorption of calcium increased during the intake of 100 gm lactose in two patients and remained unchanged in the third compared to control values. During the intake of 50 gm lactose contained in milk or given with calcium gluconate the absorption of calcium was similar. The endogenous fecal calcium was similar to that in control studies when 100 gm lactose was given, during the intake of milk containing 50 gm lactose and during the intake of lactose given with calcium gluconate. The studies showed that in lactase deficiency, lactose had no effect on the balance of calcium, on the absorption of calcium nor on the endogenous fecal calcium. The patients adapted to gradually increasing amounts of milk and have consumed one quart of milk for 4-5 years without undesirable side effects.

42.2

LUMBAR VERTEBRAL BONE DENSITY STUDIES IN A SELECTED MALE POPULATION. F. Hosain, * L.A. Spitznagle, * L.G. Raisz, * R.P. Spencer, G.A. McCurdy, * P.A. Barton, * D.M. Malcolm, * J.K. Drost. * Univ. Connecticut Health Ctr., Farmington, CT 06032

Concern about postmenopausal bone mineral loss in women has overshadowed recognition that males can be affected by osteopenias. We studied 43 males referred for lumbar vertebral bone density evaluation (because of fractures, radiographic changes, medication history or symptoms). The methodology utilized a Norland dual beam (Gd-153) rectilinear scanner. The densitometer was standardized against both a mineral composite and human vertebrae (scanned under a water bath). Vertebrae were ashed to determine actual mineral content. Age range of the men was 20-83 years, with a mean of 56 and a mode of 65 years. Average density of L-2, L-3 and L-4 in the group showed little difference (0.923, 0.981, 0.939 gm/cm$^2$ for areal densities). However, there was a 4 fold difference between the highest (1.448 gm/cm$^2$) and the lowest values (0.359 gm/cm$^2$) of vertebral bone mineral content. In women, the range encountered is usually under a 3 fold difference. Frequent causes of male low vertebral mineral content have fallen into 4 categories. 1. Hematopoietic (such as the lymphomas). 2. Medication effects (as with steroids). 3. Hypogonadism. Androgen lack by failure to develop, orchiectomy, or possibly use of antiandrogens, may be involved. 4. Idiopathic. This may be a heterogenous class awaiting study. (Supported in part by USPHS CA 17802).

42.3

1,25-DIHYDROXYVITAMIN $D_3$ RECEPTORS AND TESTIS CELL FUNCTION. B. C. Osmundsen*, M.B. Anderson*, and M. R. Walters*. (SPON: N. Kreisman). Tulane Med. School, New Orleans, LA 70112.

These studies investigated the cell localization of 1,25-dihydroxyvitamin $D_3$ [$1,25(OH)_2D_3$] receptors in the seminiferous tubules of the rat testis and whether changes in testicular function affect their levels. When germ cell division was abolished with minimal effect on the Sertoli cells (5 d cryptorchidism and 35 d busulfan), $1,25(OH)_2D_3$ receptor levels/g testis were unchanged. However, receptors/testis decreased modestly ( 25%, $P<0.05$) in proportion to the testis wt loss. When the busulfan-treated rats recovered normal germ cell function (85 d), both testis wt and $1,25(OH)_2D_3$ receptors/testis also normalized. In 50 d cryptorchidectomized rats, where substantial Sertoli cell damage accompanies the loss of germ cell function, $1,25(OH)_2D_3$ receptor levels were significantly ($P<0.001$) reduced to only 34.8±11.8% of control. Sertoli stimulation by FSH injection yielded a 2-3 fold increase ($P<0.02$) in receptors/testis and receptors/g testis. Conditions affecting Sertoli cells influenced receptor density most, providing evidence for roles of $1,25(OH)_2D_3$ therein. Further studies are required to fully establish whether $1,25(OH)_2D_3$ receptors also reside in some germ cells because the treatments affecting germ cells may also affect the Sertolis and because of previous reports of the absence of receptors therein. In conclusion, these functional studies establish the Sertoli cell as a primary site of $1,25(OH)_2D_3$ action in the testis.

42.4

IHIBITORY EFFECT OF CALCITONIN GENE-RELATED PEPTIDE (CGRP) ON GASTRIC INHIBITORY PEPTIDE (GIP)-INDUCED INSULIN RELEASE FROM CULTURED ADULT RAT ISLET CELLS. J. Ishizuka*, G.H. Greeley, Jr., C.W. Cooper*, J.C. Thompson and P. Singh. Depts of Surg and Pharmacol, The Univ of TX Med Branch, Galveston, TX 77550.

We have used short-term cultured adult rat pancreatic islet cells in order to examine the action of GIP and/or CGRP on glucose-stimulated insulin release. Methods. Islet cells were prepared by trypsin-collagenase digestion of rat pancreas. Cells were cultured for 2 d in NCTC 135-Medium-199 (10% fetal calf serum, 16.7 mM glucose and 50 µg/ml Gentamicin) to eliminate fibroblastoid and exocrine cells. Cells cultured for 4 d were pre-incubated for 1 h with KRB containing 0.2% BSA and 2.7 mM glucose, followed by addition of secretagogues for 1 h. Insulin was measured in the incubates and cells. Results. Glucose stimulation of insulin release from cultured cells was dose-dependent. GIP augmented glucose-mediated insulin release, but CGRP inhibited it. The inhibitory effect of CGRP on insulin release was greater with GIP + glucose than with glucose alone. Electron microscopy of cultured cells showed intracellular contacts between structurally intact A, B, and D cells. Conclusion. We have developed a preparation of cultured cells of rat pancreatic islets that is suitable for studying the direct effects of hormones on the cells. Our findings suggest that the inhibitory site of action of CGRP and the stimulatory site of action of GIP are mediated by endocrine cell receptors and not by neurotransmitters, and that CGRP may be an anti-incretin factor.

42.5

EFFECT OF PEPTIDE YY AND NEUROPEPTIDE Y ON 2-DEOXY-D-GLUCOSE-INDUCED RELEASE OF INSULIN, GLUCAGON AND PANCREATIC POLYPEPTIDE. George H. Greeley, Jr., Felix Lluis*, Guillermo Gomez*, and James C. Thompson. Department of Surgery, The University of Texas Medical Branch, Galveston, Texas 77550.

Peptide YY (PYY), a gut peptide, and neuropeptide Y (NPY) are two new members of the pancreatic polypeptide (PP) family. IV administration of 2-deoxy-d-glucose (2-DG) results in the release of insulin, glucagon and PP. The purpose of this study was to examine the effect of PYY and NPY on the action of 2-DG. Methods. Seven dogs were given 2-DG (90 mg/kg, IV) for 5 min alone or in combination with PYY or NPY (400 pmol/kg-h, IV) for 60 min. Blood was collected at regular intervals. Results. Values ($\bar{X}$ ± SEM) are expressed in integrated release over basal. (* = $p<0.05$ alone).

| | 2-DG Alone | 2-DG + PYY | 2-DG + NPY |
|---|---|---|---|
| Plasma Insulin(ng.min/ml) | 68.6±19.0 | 30.4±10.4* | 47.4±14.4 |
| Plasma Glucagon(ng.min/ml) | 1.4±0.2 | 1.2±0.3 | 1.9±0.5 |
| Plasma PP(ng.min/ml) | 4.6±0.8 | 2.4±0.8* | 3.5±1.1 |

Conclusions. PYY, but not NPY, inhibits the release of insulin and PP induced by 2-DG. The release of glucagon is not affected by PYY or NPY.

42.6

β-ENDORPHIN-INDUCED HYPERGLYCEMIA IN RABBITS: THE EFFECTS OF A GLUCOSE OR ARGININE CHALLENGE ON INSULIN AND GLUCAGON. R.L. Schleicher*, R.K. Chawla*, P.A. Coan*, D. Martino-Saltzman* and D.C. Collins. Dept. Med., Emory Univ. Sch. Med. & VA Med. Ctr., Decatur, GA 30033

The effects of β-endorphin (BE) on glucose, insulin, and glucagon levels were studied in fasted adult rabbits. BE (31 µg/kg BW; iv), injected immediately prior to an iv bolus of glucose (0.7 g/kg BW), significantly delayed glucose clearance ($p<0.05$). Plasma insulin levels were lower in the BE group ($p<0.05$). Glucagon levels were unchanged by glucose in either the control or BE-treated group (x ± SE = 102.8 ± 4 pg/ml, 0-120 min). A 30 min infusion of L-arginine (ARG; 13 mg/kg BW/min;iv) in control rabbits produced a rapid (10 min) increase in plasma insulin and glucagon; plasma glucose levels were not altered (x ± SE = 94.5 ± 1 mg/dl). Administration of BE (31 µg/kg BW; iv) at the start of the ARG infusion resulted in a rapid (10 min) and long-lasting (60 min) hyperglycemic effect and a decrease in insulin levels (10-20 min; $p<0.05$). Glucagon levels were elevated (10-30 min; $p<0.01$) in the BE-treated rabbits compared with controls (x ± SE = 484 ± 43 vs 275 ± 45 pg/ml). These data suggest BE reduces the normal insulin response to glucose and ARG and does not affect glucagon release in glucose-stimulated animals but potentiates ARG-stimulated glucagon release. (Supported by NIH Grants AM-13129 and AMRBAMO-7298-0682.)

42.7

CHANGES IN OXYTOCIN AND VASOPRESSIN CONTENT IN RAT PITUITARY AND HYPOTHALAMUS FOLLOWING PANTETHINE TREATMENT. G.L.Ong*, C.Miaskowski* and J.Haldar. Department of Biological Sciences, St. John's University, Jamaica, NY 11439

Pantethine, a Cysteamine precursor has been shown to cause depletion of somatostatin and prolactin in the hypothalamus and pituitary respectively (Reichlin, 1985). The purpose of this experiment was to determine whether pantethine had a similar effect on oxytocin (OT) and vasopressin (VP) content of the hypothalamus and pituitary. Experiments were done with five groups of male Long Evans rats. Group I served as controls, and the othrs received an i.p. injection of pantethine (mg/100 gm B.W.) in the following doses: 73.35 (II), 146.7 (III), 293.4 (IV) and 586.8 (V). Three hours after the injection, rats were sacrificed and pituitary and hypothalami were isolated, homogenized in 0.1 N HCl and centrifuged. OT and VP content were determined in extracted samples by radioimmunoassay. Our results show: (1) both OT and VP were depleted in the pituitary and hypothalamus, (2) OT content in the pituitary and hypothalamus was depleted by at least 46.3% and by at least 39.2% respectively, with all doses of pantethine and (3) depletion of OT was more pronounced than VP. It would appear from this data, that pantethine has a similar action on two other brain peptides, namely OT and VP. (Supported by NSF PCM 8312200).

42.8

RELATIONSHIP OF SERUM $K^+$ TO TSH RESPONSE TO TRH IN MEN. V. Wahby*, E. Milad*, J. Gilden*, C. Barsano*, S. Singh*, and F. Ellyin* (Spon: T. Hansen). VA Med Center and Chicago Medical School, Chicago, IL 60064.

The relationship of serum $K^+$ to TSH response to TRH is not quite clear. This is significant when TRH tests are performed in subjects receiving drugs that alter serum $K^+$ levels, e.g. certain diuretics.

Normal euthyroid men (N=37) age 36.7±2.3 yrs (mean ±SE) received each 500 ug TRH IV. $K^+$ was measured by ion-specific electrodes; TSH by RIA. The group was divided into 2 subgroups: A (N=19) & B (N=18) with serum $K^+$ levels smaller and larger than the group's mean (4.1±0.04 mEq/l) respectively. The subgroups were similar in: age, height, weight, serum Na, Ca, $PO_4$, $TT_4$, $TT_3$ & $FT_4$. Mean $K^+$ levels were 3.7 ± 0.03 and 4.4 ± 0.06 mEq/l ($p<0.001$); mean TSH was 11.04±1.3 uU/ml & 7.4±0.5 uU/ml ($p<0.02$) for Groups A & B respectively.

COMMENT: Lower levels of serum $K^+$ may be accompanied by increased TSH responses to TRH. If this finding is confirmed in larger subject samples, then care should be exercised in interpreting TRH test results in patients receiving medications that may alter serum $K^+$ levels.

42.9

AMINO TERMINAL PEPTIDE OF GROWTH HORMONE ENHANCES INSULIN ACTION IN VIVO BY INCREASING GLUCOSE UPTAKE IN SKELETAL MUSCLE. Carl E. Mondon, Gerald M. Reaven*, and Luciano G. Frigeri*. VA Med. Ctr., Palo Alto, CA 94304 and Scripps Mem. Hosp., La Jolla, CA 92037

In vivo studies have demonstrated that infusion of glucose to the intact rat (425-475g) during an insulin suppression test resulted in steady state serum glucose (SSSG) levels of 256 mg/dl and addition of amino acid residues 32-46 of human growth hormone (hGH 32-46) did not further suppress SSSG concentration. Infusion of insulin to yield steady state serum insulin levels of 70μU/ml lowered SSSG to 119 mg/dl. Under these conditions, addition of hGH 32-46 resulted in a further decrease in SSSG to 87 mg/dl ($p<.01$). To determine whether this potentiation of insulin action was manifested on the liver and/or skeletal muscle, livers and hindlimb skeletal muscle were isolated and perfused with a recirculating blood buffer media. Livers perfused without added hormones release 13.1μmol/glucose/g liver and this efflux was suppressed by insulin to 4.2μmol/g liver and to comparable levels by insulin + hGH 32-46. Uptake of glucose by hindlimb skeletal muscle was expressed as a metabolic clearence (k) and averaged 6.67 ul/min/g muscle when perfused without added hormone. Addition of insulin enhanced k to 8.17 ul ($p<.01$) and this increase was further enhanced to 9.24 ul ($p<.05$) with added hGH 32-46. These findings suggest that potentiation of insulin action by hGH 32-46 occurs primarily by facilitating glucose uptake by peripheral tissues and not by liver.

42.10

DETECTION OF GLYCOSYLATED GROWTH HORMONE IN THE HUMAN PITUITARY GLAND. Y.N. Sinha and U.J. Lewis.* Whittier Institute for Diabetes and Endocrinology, La Jolla, CA 92037

Although several of the pituitary hormones are glycoproteins, growth hormone (GH) and prolactin (PRL) were never thought to be so. Nevertheless, a glycosylated form of PRL was recently discovered (Lewis et al., PNAS 81:385, 1984). We now report detecting glycosylated GH (G-GH) with our newly-developed lectin-binding RIA (Sinha and Lewis, Endocrinology, 118(Suppl.):000, 1986). The method consists of reacting pituitary extracts with sugar-binding lectins immobilized on plastic tubes. Glycoproteins that bind to the lectin are next reacted with GH-specific antibodies. The degree of antibody binding is quantitated by the use of a labeled second antibody. With this method, we detected Concanavalin A-binding hGH in each of the 23 cadavar pituitaries we analyzed. The concentration of glycosylated human GH (G-hGH) amounted to nearly 10-15% of total hGH in the pituitary gland, i.e., 0.5-1 mg per pituitary. Chromatography of pituitary extracts on Sephadex G-100 revealed a G-hGH peak approximately 4,000-5,000 daltons greater in $M_r$ than the usual hGH. However, a great proportion of G-hGH was present in aggregated (void volume), dimeric, and cleaved forms. Analysis with SDS-PAGE and Western blotting also revealed a 26,000-27,000 $M_r$ GH-immunoreactive band in both human and murine tissues which may be G-GH. We conclude that there are glycosylated forms of GH in the human and murine pituitary glands. Supported by NIH Grant No. AM-32311.

42.11

**ADENOSINE ANALOGS ENHANCE THE SECRETION AND SYNTHESIS OF ß-ENDORPHIN AND DIMINISH THE SECRETION AND SYNTHESIS OF PROLACTIN FROM CULTURED RAT ANTERIOR PITUITARY CELLS.** **J.R. Dave, J.C. Bisserbe* and R.L. Eskay*, LCS, NIAAA, DICBR, Bethesda, MD 20892.**

Adenosine is known to regulate a variety of physiological processes via two distinct membrane-associated receptors (Ra and Ri). We have earlier reported that adenosine and its analogs stimulate adenylate cyclase activity and ß-endorphin secretion from mouse-derived anterior pituitary tumor cells (AtT-20's). The objectives of this study were to determine if i) adenosine, by acting as a secretogogue, would stimulate the synthesis and release of ß-endorphin in cultured anterior pituitary (AP) cells and ii) the observed effects of adenosine on corticotrophs are specific only to corticotrophs. We have evaluated the effect of adenosine analogs, cyclo-hexyl-adenosine (CHA) and N-ethyl-carboxamidoadenosine (NECA), on the secretion of ß-endorphin and prolactin, and pro-opiomelanocortin (POMC) and prolactin messenger RNA (mRNA) levels in primary-cultured rat AP cells. The incubation of AP cells with various concentrations of CHA ($10^{-7}$ to $10^{-3}$ M) for 1 hr produced a dose-related increase in ß-endorphin secretion. A maximal stimulation of 250% above controls was observed at $10^{-3}$M CHA. The incubation of AP cells with CHA for 24 hr increased POMC mRNA levels in a dose-related manner. A maximal increase in POMC mRNA levels (175% above the controls) was observed at $10^{-3}$M CHA. Incubation of AP cells with CHA decreased prolactin secretion in a dose-related manner. At $10^{-7}$M CHA a 20% decrease in prolactin secretion and a 60% reduction in prolactin mRNA levels were observed. These results suggest that adenosine has opposite regulatory roles in corticotrophs and lactotrophs. Furthermore, adenosine may regulate the synthesis and secretion of POMC derived peptides from corticotrophs via an Ra type adenosine receptor and the synthesis and secretion of prolactin from lactotrophs via an Ri type adenosine receptor.

42.12

POTENTIATED CORTISOL SECRETION AFTER REPEATED HEMORRHAGE IS ASSOCIATED WITH INCREASED RESPONSES OF VASOPRESSIN AND PLASMA RENIN ACTIVITY. M.P.Lilly*, E.J.DeMaria* and D.S.Gann. Dept. of Surgery, Brown University/RI Hospital, Providence, RI 02902

We have shown potentiated responses of cortisol secretion(F) and ACTH to the second of 2 small hemorrhages(H) separated by 24h. Since vasopressin(AVP) and angiotensin increase ACTH release, we studied AVP and renin activity(PRA) in repeated H. Awake trained dogs(n=7) with chronic adrenal vein catheters were bled 10% of measured blood volume(BV) over 3min(H1). Blood was reinfused at 30min and the H repeated 5h later(H2). F was measured by HPLC; arterial ACTH, AVP and PRA by RIA. Data were analyzed by ANOVA(@=p<.05 vs control,*=p<.05 vs H1).

| | | Control | 4min | 8min | 10min |
|---|---|---|---|---|---|
| F(ug/min) | H1 | 1.1±0.3 | 1.4±0.6 | 1.7±0.6 | 3.5±1.1@ |
| | H2 | 1.1±0.2 | 1.1±0.2 | 2.8±0.8 | 8.5±3.0@* |
| ACTH(pg/ml) | H1 | 25.0±2.5 | 17.7±5.8 | 27.0±3.8 | 31.2±4.9 |
| | H2 | 27.5±7.1 | 32.7±9.1 | 39.2±8.2 | 60.0±27.3@* |
| AVP(pg/ml) | H1 | 3.1±0.6 | 3.7±0.7 | 4.5±0.6 | 4.2±0.6@ |
| | H2 | 3.5±0.7 | 5.0±0.7 | 10.2±3.8 | 11.6±5.7@* |
| PRA | H1 | 1.9±0.3 | 2.9±0.3 | 3.4±0.4 | 3.3±0.6@ |
| (ngAI/ml/h) | H2 | 2.1±0.3 | 3.9±0.5* | 4.0±0.5 | 3.9±0.5@ |

Resting BV and heart rate and mean arterial pressure responses in the Hs were not different. F, ACTH, AVP and PRA responses are greater to H2. Cross-correlation showed no temporal lag between responses of ACTH and AVP or PRA. Increased responses of AVP and PRA thus may be involved in the increased ACTH response seen after repeated H. (Support by NIH AM26831 & GM27946)

42.13

CELLULAR UPTAKE OF THYROXINE FROM SERA OF SUBJECTS WITH EUTHYROID HYPERTHYROXINEMIA. Williams, I.K.*, J. Wortsman*, B.C. Nisula* & B.N. Premachandra. VA Med. Ctr. & Wash. Univ., St. Louis, Mo., SIU Med. School, Springfield, Ill. and NIH, Bethesda.

The elevation of thyroid hormone sensitive sex hormone binding globulin (SHBG) in the sera of some individuals with dysalbuminemic hyperthyroxinemia suggested that uptake of thyroxine ($T_4$) may be elevated from sera of hyperthyroxinemic subjects. To examine this possibility, in vitro techniques were used to measure 1 min. and 2 hr. $T_4$ tracer uptake (at 37° C) by red blood cell (RBC) and lymphocytes from $^{125}I$-$T_4$ equilibrated hyperthyroxinemic sera [from subjects with inherited thyroxine binding globulin (TBG) excess or familial dysalbuminemic hyperthyroxinemia (FDH)]. Total $T_4$ concentration in hyperthyroxinemic sera varied from 11.0 - 26.2 µg/dl (normal 5.5 - 12.0 µg/dl), whereas free thyroxine concentration (1.3 - 2.0 ng/dl) was within the normal range (0.9 - 2.3 ng/dl). The 1 min. and 2 hr. RBC $T_4$ uptake from FDH sera (serum $T_4$ concentration X % uptake) was 0.95 ± 0.18 and 3.54 ± 0.67, respectively, and these values were higher ($p < 0.01$) than respective control values (0.52 ± 0.08 and 2.4 ± 0.32). Additionally, the 1 min. and 2 hr. lymphocyte $T_4$ uptake from FDH sera was 0.67 ± 0.11 and 4.91 ± 1.69, respectively; these values were significantly greater than the control $T_4$ uptakes at 1 min. and 2 hrs. which were 0.31 ± 0.08 and 2.26 ± 0.54, respectively. Similarly, the 2 hour absolute RBC $T_4$ uptake in high TBG sera (2.94 ± 0.42) was greater than in normals (2.40 ± 0.32).

Summary: Cellular $T_4$ extraction from sera with elevated $T_4$ binding was significantly greater than the uptake noted from control sera despite normal $FT_4$ concentration in both cases.

42.14

DOES A DEFECT EXIST IN A SPECIFIC SEROTONERGIC BRAIN AREA OF THE OBESE ZUCKER RAT? Johnny R. Porter, David Roane*, Douglas White*, and Arthur D. Hartman. La. St. Univ. Med. Ctr. New Orleans, La. 70119.

In the present study we choose to compare a functionally specific serotonergic area of the brain, the pineal, to a functionally more diffuse serotonergic area, the hypothalamus. Obeseand lean female sibling rats were sacrificed by decapitation between 9 and 10:00 AM. Hypothalami and pineals were rapidly dissected, weighed, homogenized in 0.1M perchloric acid. Protein determinations were carried out on diluted aliquots of whole sonicated homogenates. Supernatants were prepared by centrifugation of homogenates at 12,000 X g for 5 min. Concentrations of serotonin and 5-hydroxyindole acetic acid (5-HIAA) were determined by high performance liquid chromatography (HPLC) of supernatants followed by electrochemical detection of separated biogenic amines in column eluents. Average body weights were 434 g for obese animals vs 255 for lean animals ($p<0.01$). No significant differences were found between lean and obese organ weights or biogenic amine concentrations with the exception of pineal serotonin. Pineal serotonin was almost double (lean = 226 ng/100 µg protein; obese = 147 ng/100 µg protein) in lean animals compared to obese animals ($p<0.05$). These results show a specific defect in one brain serotonergic system of the obese rat and suggest the possibility that serotonin concentrations in other specific areas of the brain (e.g. Raphe nucleus) may be altered in the obese Zucker rat.

42.15

IMMUNOREACTIVE ATRIAL NATRIURETIC PEPTIDE IN EXTRACTED AND NON-EXTRACTED RABBIT PLASMA. Wilson, N., D. Feuchuk*, C.A. Courneya*, and R. Keeler*. Dept. of Physiology, Faculty of Medicine, University of B.C., Vancouver, B.C., Canada.

In a radioimmunoassay using the Peninsula (RAS 8798) antiserum, we compared non-extracted with extracted (Sep-Pak, C-18, Waters) rabbit plasma using two eluent systems: 80% methanol:4% acetic acid (A) and 80% methanol:0.1% trifluoroacetic acid (B). Recovery was measured by addition of known amounts of atriopeptin III (AIII) to plasma. In A, the recovery was 45-57%; non-extracted plasma was 36.4±2.4 pg/ml, while following extraction ANP was 14.8±1.5 pg (corrected for recovery, n=15). In B, recovery was 78-87%; non-extracted levels - 38.8±3.4 pg/ml, while extracted (corrected, n=15) ANP concentrations were 19.9±2.5 pg/ml. Chromatography of non-extracted concentrated rabbit plasma on Sephadex G-100 (9 x 400 mm, 4°C) resulted in two approximately equal immunoreactive peaks: the first - in the Vo region, the second eluting with the Ve of iodo-AIII. Application of the extracted (System B) plasma to the same column yielded one immunoreactive peak, corresponding to Ve of iodo-AIII. Chromatography of the portion which was not adsorbed on Sep-Pak resulted in one immunoreactive peak in the Vo region. Thus the total immunoreactive ANP in non-extracted rabbit plasma detected by RAS 8798 consists of at least two different molecular species: one corresponding to AIII or a related molecule, while the other is a larger form. Funded by MRC and Can. Heart Fndn.

42.16

LUNG-DERIVED GROWTH FACTORS: EVIDENCE FOR PARACRINE-DIRECTED FETAL LUNG DEVELOPMENT. A. M. Montes* and W. K. Morishige, Department of Physiology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96822.

The interstitial fibroblasts of the fetal lung may play a central role in early lung morphogenesis. Conditioned serum-free media (CSFM) from cultures of perinatal rat lung fibroblasts contained two mitogenic activities, which were separable by Sephadex gel filtration and exhibited specificity for different cell types: lung-derived growth factor (LDGF) stimulated thymidine incorporation in chick embryo fibroblasts while pneumocyte-stimulating activity (PSA) selectively stimulated pneumocyte proliferation in pneumocyte-enriched rat lung cell cultures, as determined by autoradiography. The presence of yet a third mitogen in CSFM was suggested by the finding that, whereas LDGF alone was not mitogenic in the abscence of a competence factor, unprocessed CSFM was fully mitogenic in rat lung fibroblasts. The existence of these fetal paracrine factors provide an important first step toward a clear understanding of the mechanisms regulating embyonic lung development.

42.17

INHIBITION OF FORSKOLIN-ACTIVATED ADENYLATE CYCLASE BY FORSKOLIN ANTIBODIES R.J. Ho, L.T. Ho* and R.E.Garola* Dept. of Biochem., Univ. of Miami Sch. of Med., Miami, FL 33101.

Forskolin antibodies generated by goat have been partially purified through ammonium sulfate (40% sat.) precipitation, DEAE Affigel Blue column (2.5x30 cm) and immunoadsorption column (0.7x5 cm). Like forskolin antisera, antiforskolin IgG so obtained gave a positive test in ELISA and RIA. ELISA was performed using immobilized forskolin-human albumin conjugate as the immunogene and HRP-rabbit anti-goat IgG as the marker. RIA was based on the binding of $^3H$-forskolin to antibodies following separation of free from bound $^3H$-forskolin by dextran coated charcoal. A third criteria for evaluating forskolin antibodies has been developed; this is based on its inhibition of forskolin-activated adenylate cyclase. The amount required to demonstrate such inhibition depends on the concentration of forskolin used as activator. Adipocyte plasma membrane (20 µg) was incubated in the presence of 91 µM epinephrine, 20 µM Gpp(NH)p with and without forskolin and with and without antiforskolin IgG for 10 min at 30°C. Forskolin was preincubated with antibodies at 4°C for 60 min before the enzyme assay. At 0.3 µM forskolin, 120-240 µg of IgG/tube inhibited 30-50% of forskolin-activated enzyme. Application of such antibodies in the study of the mechanism of adenylate cyclase activation by forskolin is in progress (partly supported by NSF under grant number DCB-8417472).

42.18

IMMUNOPHYSIOLOGY OF THE MACROPHAGE IN ACUTE PANCREATITIS. E. Sherwood*, D. Williams*, E. Jones*, R. McNamee*, I.W. Browder* and N.R. Di Luzio. Depts. of Physiology and Surgery, Tulane University School of Medicine, New Orleans, LA 70112.

The protective role of macrophage activation in acute pancreatitis was assessed by feeding, female, 4-5 week old, Swiss Webster mice a choline deficient diet supplemented with 0.5% DL-ethionine (CDE diet) for 3 days to induce pancreatitis. Glucan, a potent macrophage stimulant, was administered subcutaneously (5 mg/mouse) at the time of initiating the CDE diet. Control mice received 5% (w/v) dextrose in the same regimen. By day 3, the CDE diet induced severe pancreatitis, in control mice, as indicated by elevated serum amylase levels and destruction of pancreatic architecture. Plasma and peritoneal trypsin levels were also significantly ($p<0.05$) elevated by 290% and 71%, respectively, in control mice. Glucan mice were protected by 43 and 846% increases in trypsin-binding activity (TBA) in plasma and the peritoneal cavity, respectively, which was reflected by enhanced longterm survival (68 vs 14%). We also observed a significant ($p<0.05$) 61% increase in interleukin-1 (IL-1) production by splenic macrophages from glucan-treated mice. Enhanced IL-1 secretion is indicative of macrophage activation and is a potent inducer of hepatic $\alpha_1$-antitrypsin production. The present study shows macrophage activation to be beneficial in acute pancreatitis. The protective effect appears to be mediated by increased levels of $\alpha_2$ macroglobulin ($\alpha_2M$) and enhanced clearance of trypsin-$\alpha_2M$ complexes from the vasculature and peritoneal cavity.

42.19

HISTOLOGIC AND HEMATOLOGIC ALTERATIONS IN RATS WITH AN IMPLANTED OSMOTIC PUMP INFUSING ENDOTOXIN. JA Spitzer[1], CS Walters[1*], LJ Vial, Jr.[1*], S Pross[2*], C Newton[2*] and H Friedman[2*], Louisiana State Univ. Med. Ctr., New Orleans, LA[1] and Univ. of South Florida Coll. of Medicine, Tampa, FL.[2]

Continuous infusion of endotoxin (ET) via an implanted osmotic pump results in marked, but transient alterations in physiologic and metabolic parameters. Recent studies demonstrated that by 5-7 days after pump implantation the blastogenic responsiveness of spleen cells to T and B cell mitogens was essentially abolished. Spleen size also increased greatly and paralleled hematologic alterations. Rats with NaCl-dispensing pumps showed a slight increase in spleen size and less hematologic change. In the spleen, lymphoid activity was evaluated by the number and size of lymphoid follicles and germinal centers, hematopoietic activity by the number of megakaryocytes and erythroid precursors. The amount of lymphoid tissue and hematopoiesis declined through day 5 in both ET- and NaCl-infused rats, then rose to normal or above normal levels. Peripheral blood findings paralleled histologic observations e.g.l. great decrease in platelets from day 2-5, returning to normal by day 10, and 2, reticulocytosis by day 10. There was also initial leukocytopenia, followed by leukocytosis. The dramatic monocytosis on day 5 is likely to have included macrophages. Thus, slow continuous infusions of non-lethal doses of ET results in marked changes in splenic cellularity and concomitant hematologic changes, not unlike those associated with clinical infections. Supp. in part by GM30312 and GM32654 (JAS).

42.20

THE NK RESPONSE CAN BE LEARNED. Raymond N. Hiramoto, H. Brent Solvason*, Nancy S. Hiramoto*, and Vithal K. Ghanta. Univ. of Alabama at Birmingham, Birmingham, AL 35294.

A paradigm known as taste aversion learning was used to condition the natural killer (NK) cell response. In this paradigm saccharin, the conditioned stimuli (CS) was paired with LiCl an unconditioned stimuli (US) for gastrointestinal upset. We have combined both saccharin (0.1%) and LiCl (125 mg/kg) as the CS and paired this with poly I:C (20 µg/mouse) as the US (Jenkins et al, Bull. Psychonomic Soc. 21:485 1983). We show that in suitably conditioned mice the CS (saccharin + LiCl) alone increased the NK response in the spleen. The NK response was measured by the $^{51}Cr$ release assay for each individual animal at effector:target (E:T) cell ratio of 200:1, 100:1 and 50:1. The CS alone recalled 71, 63, and 61% of the maximum NK response seen in the control group given the US (poly I:C) alone. The response was statistically significant $p < 0.002$ at all E:T ratios tested. Our studies show the magnitude of the conditioned response was small but readily reproducible. Repeated association was not needed in that one association trial and one exposure to the CS could recall the response and the response could be extinguished by repeated exposure to the CS. Finally, the experiments could be completed in 7 days and small numbers (5-6) of animals/group could be used to attain statistically significant data. Supported by NIH grants MH40566 and CA37570.

42.21

MASS, FIBER NUMBER AND CROSS-SECTIONAL AREA OF HINDLIMB SKELETAL MUSCLES FROM C57BL/6 MICE AT 12 AND 28 MONTHS OF AGE. Timothy P. White, Kathryn I. Clark*, and Susan C. Kandarian*. Dept. of Kinesiology, The University of Michigan, Ann Arbor, MI 48109-2214.

We tested the hypothesis that skeletal muscle of 28-mo (aged; N=15) C57BL/6 mice would have smaller mass, fewer fibers and smaller cross-sectional area than 12-mo (adult; N=20) mice. This adaptation would be consistent with a reduced ability to produce muscular force, an ubiquitous age-related change. Data were obtained from the extensor digitorium longus (EDL), soleus, and plantaris muscles. Fibers were counted following nitric acid digestion of connective tissue. Compared to 12-mo values, muscle mass of 28-mo mice was 80% for EDL, 90% for soleus and 80% for plantaris muscles ($p < 0.05$). Total fiber number was not different due to age in all muscles; the mean values for EDL, soleus and plantaris muscles of 28-mo mice were 100, 95 and 94% of the 12-mo values, respectively ($p > 0.05$). Preliminary analysis of frequency distributions of fiber cross-sectional area reveals a higher proportion of fibers with small areas in muscles of 28-mo vs. 12-mo mice. Supported by NIH-National Institute on Aging AG-06130.

42.22

REPEATABILITY OF THE PULMONARY FUNCTION RESPONSE TO OZONE. John F. Bedi*, Deborah M. Drechsler-Parks*, and Steven M. Horvath, Institute of Environmental Stress, University of California, Santa Barbara, CA 93106.

Eight men and 8 women, average age 62.8 years, participated in three 2-hour exposures to 0.45 ppm ozone at WBGT temperature of 19.1°C. Subjects alternated riding a bicycle ergometer for 20 min at a workload which evoked an average minute ventilation of 26 L BTPS, with 20-min rest periods. Forced expiratory maneuvers were performed pre- and post-exposure. Each exposure was separated by a minimum of 7 days with an average time of 17.2 days between the second and third exposure. Linear regression of the pre-exposure measures between exposures resulted in slopes near 1 (0.974 to 1.06), near zero intercepts (-0.22 to 0.01) and correlation coefficients near 1 (0.92 to 0.99). Comparison of either the decrement or percentage change in forced vital capacity, forced expiratory volume in 1 sec, and forced expiratory flow 25-75% resulted in slopes ranging from 0.2 to 0.92, intercepts from 0.14 to 7.7, and correlation coefficients from 0.21 to 0.66. Four subjects did not respond to the ozone exposure at all, while 3 subjects responded to each exposure. The remaining subjects responded to at least one exposure by a significant decrease in one of the measured parameters. Older individuals who are insensitive to the effects of smog during one episode may respond to future exposures.

42.23

PULMONARY FUNCTION RESPONSES OF OLDER MEN AND WOMEN TO $O_3$. Deborah M. Drechsler-Parks*, John F. Bedi*, and Steven M. Horvath. Institute of Environmental Stress, University of California, Santa Barbara, CA 93106

The pulmonary function of 8 men and 8 women (51 to 76 yrs), all non-smokers, was measured before and after 2-hr exposures to filtered air (FA) and 0.45 ppm ozone ($O_3$). Subjects alternated 20-min periods of rest and cycle ergometer exercise at a workload predetermined to elicit a minute ventilation ($\dot{V}_E$) of approximately 25 L/min (BTPS). Functional residual capacity (FRC) was determined pre- and post-exposure. Forced vital capacity (FVC) was determined before and after exposure, and 5 min after each exercise period. Minute ventilation ($\dot{V}_E$) was measured during the last 2 min of each exercise period, and heart rate was monitored throughout each exposure. Pulmonary function data were evaluated as the percentage change from pre- to post-exposure to partially remove the effect of differences between men and women in absolute lung volume. FA induced no significant ($P>0.05$) changes in any variable. Exposure to $O_3$ induced significant ($P<0.01$) decrements in FVC, $FEV_{1.0}$ and $FEV_{3.0}$. Ozone exposure induced no significant ($P>0.05$) effect on FEF25-75% or FEF75%. Men had a higher ($P<0.05$) mean exercise $\dot{V}_E$ than women (27.9±0.29 L vs. 25.4±0.8 L; X±SD). Men and women had similar decrements in pulmonary function, even though the women inhaled less $O_3$, suggesting that women may be somewhat more responsive to $O_3$ than men. Our older subjects were less responsive to $O_3$ than young men and women we and others have studied.

42.24

DIFFERENTIAL PHYSIOLOGICAL BEHAVIOR OF RADIOPHARMACEUTICALS WITH STRUCTURALLY ANALOGOUS CHEMICAL COMPOUNDS. P. Hosain*, R. P. Spencer, and F. Hosain*. University of Connecticut Health Center, Farmington, CT 06032, and Center for Allergy and Immunology, Hartford, CT 06105.

Cationic species of technetium-99m, following reduction of pertechnetate, form complexes with many compounds, e.g. methylenediphosphonate & diethylenetriaminepentaacetate used for bone and renal imaging respectively. We previously demonstrated that the two phosphate moieties, and even the presence of phosphorus atoms, was not required in such a bone seeking agent. Our recent studies indicated that the presence of OH with the phosphate-type moiety is important, since substitution of a $CH_3$ group in place of the OH in a phosphonic acid analogue of serine greatly altered the bone seeking properties of the compound. The present study was carried out with two analogous compounds. One contained 3 phosphate groups $N(CH_2(PO(OH)_2)_3$ and the other had 3 carboxyl groups $N(CH_2COOH)_3$. Both compounds were readily labeled with Tc-99m, but the former behaved like a bone seeking agent whereas the later was excreted in the urine. Presence of OH facilitated binding of Tc-99m in both the compounds, but the former one is likely to have a free OH (not engaged in chelation of cationic species of Tc-99m) which can then participate in exchange and adsorption phenomenon with the hydroxyapatite leading to bone uptake of radioactivity. (Supported in part by USPHS CA 17802).

42.25

IS 24-HYDROXYLATION OF 1,25-DIHYDROXYVITAMIN $D_3$ and 25-HYDROXYVITAMIN $D_3$ CATALYZED BY THE SAME ENZYME? M. Burgos-Trinidad* and H. F. DeLuca. Department of Biochemistry, University of Wisconsin, Madison, WI 53706.

The first inactivation step in the metabolism of 1,25-dihydroxyvitamin $D_3$ ($1,25-(OH)_2D_3$) is presumably 24-hydroxylation. Similarly, 25-hydroxyvitamin $D_3$ ($25-OH-D_3$) is 24-hydroxylated to 24,25-dihydroxyvitamin $D_3$ ($24,25-(OH)_2D_3$), a less active metabolite. Whether or not the 24-hydroxylation of these substrates is catalyzed by a single enzyme is still controversial. We have examined the substrate specificity of this enzyme using solubilized chick kidney mitochondrial 24-hydroxylase from vitamin D-repleted animals. The soluble fraction 24-hydroxylates both $25-OH-D_3$ and $1,25-(OH)_2D_3$ when reconstituted with NADPH, beef adrenal ferredoxin and beef adrenal ferredoxin reductase. The products of the reaction were identified by comigration with synthetic standards on straight-phase and reversed-phase high-performance liquid chromatography. $1,25-(OH)_2D_3$ markedly inhibited the production of $24,25-(OH)_2D_3$ from $25-OH-D_3$ even when present in the reaction mixture at the lowest ratio of .25:1 with the substrate. However, $25-OH-D_3$ had no effect on the production of $1,24,25-(OH)_3D_3$ from $1,25-(OH)_2D_3$ even when present at a molar ratio of 36:1 with the substrate. These results provide evidence that the 24-hydroxylations of $25-OH-D_3$ and $1,25-(OH)_2D_3$ are catalyzed by two different forms of the enzyme or by two different enzymes. (Project Program Grant No. AM-14881).

42.26

KININS GENERATED FROM SUBSTRATE PRESENT IN THE ISOLATED RAT UTERUS MEDIATE THE DIRECT OXYTOCIC EFFECT OF GLANDULAR KALLIKREIN. G. Orce*, A. Scicli, J. Stewart† and O. Carretero. Hypertension Research Division, Henry Ford Hospital, Detroit, MI 48202 and †Dept. Biochemistry, Univ. of Colorado, School of Medicine, Denver, CO 80262.

Glandular kallikrein (Kk) cleaves kininogen to generate kinins, which have oxytocic activity. Kk has been reported to have oxytocic effect independent of kinin formation (Proc. Nac. Acad. Sci. 78:6154, 1981). Specific kinin receptor antagonists (Ant) have recently been developed (Peptides 6:161, 1985). We studied whether one of these Ant, $DArg^0$-$Hyp^3$-$Thi^{5,8}$-$DPhe^7$-bradykinin blocked the oxytocic effect of Kk. The Ant, at $8.5x10^{-7}M$, displaced the dose response curves to bradykinin (Bk, $5.0x10^{-10}$ to $4.0x10^{-6}M$) and Kk ($4.7x10^{-11}$ to $8.0x10^{-9}M$) ten times to the right, while the effect of oxytocin (Oxy) was not altered. Carboxypeptidase B (CpB, a potent kininase) and antibodies to kinins also reduced the response to Kk by 65%. Removal of the Ant, the CpB or the antibodies restored the response to Kk. Multiple exposure to Kk or overnight incubation resulted in tachyphylaxis to Kk whereas the effects of Bk and Oxy remained unaltered. We conclude that most of the oxytocic activity of Kk is related to formation of kinins from substrate present in the isolated rat uterus.

## SMOOTH MUSCLE AND ENDOTHELIAL CELL PHYSIOLOGY

43.1

IMPAIRMENT OF ENDOTHELIUM DEPENDENT RELAXATION (EDR) EARLY MARKER FOR ATHEROSCLEROSIS. R.L. Jayakody*, M.P.J. Senaratne*, A.B.R. Thomson and C.T. Kappagoda. Dept. of Med., Univ of Alberta, Edmonton, Alta. Canada T6G 2R7.

Experiments were designed to characterize EDR to acetylcholine (ACH) in rings of rabbit aorta following feeding a diet containing 2% cholesterol for 4 weeks. Two groups of New Zealand White rabbits aged 8-10 (n=6) and 44-46 (n=10) weeks were studied. Age matched control rabbits were fed a standard rabbit diet. Rings of aorta were mounted for isometric tension recording in tissue baths filled with Krebs-buffer solution (37°C, 95% $O_2$-5% $CO_2$). After contracting the rings with noradrenaline (-6.0 log mol/l) the response to ACH was determined. The rings from experimental animals from both groups demonstrated significantly less relaxation to ACH than the respective controls ($p<0.05$). The young experimental rabbits had fatty streaks and plaques on the aortic intima with positive Sudan Red staining while the older experimental animals (as well as controls) did not demonstrate such changes. However scanning electron microscopy revealed abnormal endothelial cells in both experimental groups. The cholesterol levels in blood and aortic tissue were elevated in both experimental groups of animals. The aortic tissue levels were significantly lower in the older experimental animals than in the younger (181±30 vs 350±62 nmol/mg protein; $p<0.05$). The present study suggests that impairment of EDR may be an early feature of experimental atherosclerosis in rabbits.

43.2

SYNTHESIS/RELEASE OF ENDOTHELIUM-DEPENDENT RELAXATION FACTOR (EDRF) IS IMPAIRED IN EXPERIMENTAL ATHEROSCLEROSIS. C.T. Kappagoda, N. Sreeharan*, R.L. Jayakody*, M.P.J. Senaratne* & A.B.R.Thomson*. Dept. of Medicine, Univ of Alberta, Edmonton, Alberta, Canada, T6G 2R7.

This study was undertaken to determine whether the production/release of the endothelium-dependent relaxatory factor (EDRF) is impaired in atherosclerotic New Zealand White rabbits. Atherosclerosis was induced by feeding a diet containing 2% cholesterol for 6 weeks. The production/release of EDRF was assayed as follows. A 5 cm length of thoracic aorta (donor) was perfused with Krebs-bicarbonate buffer and the perfusate drained over a de-endothelialized ring of recipient aorta set up for recording isometric tension. The recipient was pre-contracted with norepinephrine (0.2 umol/l) in the perfusate. When acetylcholine (0.5, 5.0 and 15 umol/l) was added to the perfusate, the recipient relaxed in a dose dependent manner. This assay was used to compare the relaxatory responses produced in recipient rings by adding acetylcholine to donors from atherosclerotic and control rabbits. The relaxation produced by atherosclerotic donors were smaller than those generated by control donors (16.5±4.9% vs 32.7±5.3%; n=10, $p<0.05$). It is suggested that in atherosclerotic rabbits the ability of aortic endothelium to produce/release EDRF is impaired.

43.3

INCREASED ENDOTHELIAL RELAXATION AND SMOOTH MUSCLE CONTRACTION FOLLOWING ACUTE CHOLESTEROL INCORPORATION INTO ARTERIAL WALL MEMBRANES. Russell Bialecki and Tom Tulenko The Medical College of Penna. Philadelphia, Pa. 19129

The object of this study was to evaluate the functional impact of acute enrichment of arterial wall membranes with unesterified cholesterol. Carotid arteries obtained under sterile conditions from New Zealand rabbits were perfused in-vitro with an MEM-bicarbonate buffer supplemented with serum and antibiotics +/- 2:1 (mole/mole) cholesterol:phospholipid (C/PL) liposomes. The perfusate was maintained at 37°C, pH 7.4, $pO_2$ 100, $pCO_2$ 35, and the vessels perfused under 60 mmHg pressure at 4 ml/min at their in-vivo lengths. Duplicate ring segments were removed at 4 hour intervals over 36 hours and evaluated for their isometric force potential, norepinephrine (NE) sensitivity, endothelial-mediated relaxation potential, Na-pump activity and C/PL molar ratios. The results indicated that NE sensitivity increased 4-fold and endothelial mediated relaxation to acetylcholine or A23187 increased 40% after 4 hours of perfusion with the liposomal medium. This increased smooth muscle and endothelial function was associated with a concomittant increase in the C/PL ratio and decrease in Na-pump activity of the arterial segments. All parameters returned to their control levels over the remaining perfusion period inspite of continued exposure to C/PL liposomes. We conclude that acute cholesterol exposure of the arterial wall results in the incorporation of cholesterol into the cellular membranes altering membrane function and cell function. (Supported in part by NIH grants HL30497, HL07443 & AG04908)

43.5

AGE-DEPENDENT ALTERATIONS IN ENDOTHELIAL AND SMOOTH MUSCLE FUNCTION. Tom Tulenko, Robert Cox, & Donna Moisey. The Medical College of Penna., Philadelphia, Pa.

This study was designed to evaluate age-dependent changes in arterial wall vasodilator and vasoconstrictor processes. Aortic rings from Fisher 344 rats at 1, 2, 12, 24 and 30 months of age, were isolated isometrically in PSS. Dose-response studies to acetylcholine (ACh), A23187, isoproterenol (ISO), nitroprusside (NP) and forskolin (FK) were performed in rings contracted with either norepinephrine (NE) or KCl. Calcium dose-response studies in calcium depleted, KCl (60mM) activated rings were performed, and free cholesterol (FC), total phospholipids (PL), total protein and Na-pump activity were also measured. The results indicated an age-dependent decrease in sensitivity to NE, but not to 5-HT or calcium. Age-dependent reductions in relaxation to ISO, but not NP or FK were also observed. Impaired endothelial-mediated relaxations to A23187 were limited to the 30 month group with a similar, but less marked trend, to ACh. A significant increase in the FC/PL molar ratio occured in the 24 and 30 month group, and Na-pump activity demonstrated an age-dependent reduction in activity. We conclude that: (A) adrenergic but not serotonergic receptor activity and endothelial mediated relaxations are depressed with age, and (B) vasomotor pathways distal to the cell membrane are uneffected. Since the FC/PL ratio was elevated and Na-pump was depressed, it is suggested that the membrane physical state is altered in aging leading to selective changes in membrane mediated functions in the arterial wall. (Supported in part by NIH Grants AG04908 & HL30496).

43.6

PULMONARY ARTERIAL PEROXIDE METABOLISM AND THE MODULATION OF GUANYLATE CYCLASE. Michael S. Wolin, Mark Drusztman* and Theresa M. Burke*. New York Medical Coll., Valhalla, NY 10595

We have recently reported that the cytosolic form of guanylate cyclase (GC) obtained from bovine pulmonary arteries (PA) is activated through compound I, a species of catalase formed by the metabolism of peroxide, and that this mechanism may be involved in PA relaxation to peroxide. In this study we investigated peroxide metabolism in the intact PA and PA extract to develop an understanding of its control of GC and PA tone. The intact PA metabolizes $H_2O_2$ at a rate of 21±3 to 648±34 nmoles/min/gram over the concentration range of $10^{-5}$ to $10^{-3}$M in a manner that is not inhibited by the catalase inhibitor azide (0.1 mM). Glutathione peroxidase activity in the PA extract is approximately two orders of magnitude larger than the activity in the PA. GC activation and compound I of catalase (from bovine liver) formation in the PA extract occur at low nM concentrations of $H_2O_2$, whereas PA relaxation and increases in tissue levels of cyclic GMP occur over the $10^{-6}$ to $10^{-4}$M $H_2O_2$ range. Comparison of the rates of $H_2O_2$ metabolism suggest that the steady-state intra-cellular concentration of $H_2O_2$ is approximately two orders of magnitude lower than the extra-cellular concentration. Overall, the results are consistent with the activation of GC and PA relaxation by intra-cellular concentrations of $H_2O_2$ in the nM range. This mechanism of vascular regulation may be an endogenous sensor of $O_2$ tension. (supported by USPHS HL 31069 and the Am. Lung Association).

43.7

WHOLE CELL CURRENTS IN CULTURED BOVINE AORTIC ENDOTHELIAL CELLS. Margaret Colden-Stanfield*, Diana L. Kunze, Suzanne G. Eskin*, and Lydia T. Navarro*. Baylor College of Medicine, Houston, TX 77030.

Zero current potentials and whole cell currents were measured in cultured bovine aortic endothelial cells (BAEC's) utilizing the patch-clamp technique (Hamill et al., 1981). The following extracellular solution was used to identify voltage dependent ionic currents in the BAEC's: NaCl, 137mM; KCl, 5.4mM; $MgCl_2$, 1mM; $CaCl_2$, 2mM; glucose, 10mM; and HEPES, 10mM. For whole cell recordings the glass pipettes contained KCl, 145mM; HEPES, 5mM; and EGTA, 1mM. Under these conditions, BAEC's (6th-14th passage) plated 1-24 hours before study had zero current potential of -59.33 ± 7.42mV. When the voltage of the cell was held at -40mV, 10mV hyperpolarizing steps elicited a current at a membrane potential of approximately -75mV that resembled an inward rectifier potassium current. This current showed inactivating properties at the most negative steps tested (-120mV to -150mV). $BaCl_2$ at 1mM completely blocked the inward current suggesting that this current was predominantly carried by potassium ions. In approximately 60% of the cells, holding the BAEC's at -70mV and step depolarizing did not appear to activate any currents. In the others, a complex waveform was seen. The currents which composed this waveform have yet to be separated. Research supported by DHHS-NS23573 and HL23016.

43.8

**EFFECT OF EICOSANOIDS ON SHEEP PULMONARY VASCULAR AND AIRWAY SMOOTH MUSCLE.** Y. Ishihara*, J.R. Sheller* and K.L. Brigham. Vanderbilt University, Nashville, Tennessee 37232.

The effect of $PGD_2$ and a thromboxane analog ($PGH_2$-A) on the isometric tension developed by sheep tracheal segments (T), lung parenchymal strips (LP), and ring preparations of first and third order bronchi ($B_1$ and $B_3$) and on pulmonary vessels was determined in a tissue bath. Pulmonary arteries of 2-5mm ID responded to phenylephrine (PE) in a dose dependent fashion: pulmonary veins did not respond. At $10^{-4}$M PE, the tension in larger arteries was 0.78±0.28g (mean±SD) (n=7) and 0.20±0.08g in smaller arteries (n=5). However, pulmonary veins, but not pulmonary arteries, constricted to $PGH_2$-A in a dose dependent manner. At $1.4*10^{-6}$M $PGH_2$-A, larger pulmonary veins developed 0.41±0.15g (n=7) and smaller veins 0.37±0.45g (n=8) of tension. The responses in T, B, and LP to $PGD_2$ and $PGH_2$-A were normalized to the response to ACh $5*10^{-6}$M (see table).

| Tension (g) to ACh $5*10^{-6}$M | %ACh response to $1.4*10^{-6}$M $PGD_2$ | %ACh response to $1.4*10^{-6}$M $PGH_2$-A |
|---|---|---|
| T 8.2±2.9 (n=8) | 0 (n=6) | 5.8±2.9 (n=8) |
| $B_1$ 0.96±.10 (n=5) | 51±29 (n=5) | 0 (n=5) |
| $B_3$ 0.65±.13 (n=17) | 32±9 (n=5) | 1.3±2.4 (n=7) |
| LP 0.18±.03 (n=11) | 57±14 (n=5) | 326±85 (n=11) |

(mean±SEM)

Supported by NHLBI Grants No. 19153, 27274 and GM 15431.

43.9

ARACHIDONIC ACID RELEASES RELAXING FACTOR(S) FROM THE ENDOTHELIUM OF CANINE BLOOD VESSELS. U. Hoeffner and P.M. Vanhoutte, Dept. Physiol., Mayo Clinic, Rochester, MN 55905.

Exogenous arachidonic acid evokes endothelium-dependent relaxation in a number of isolated blood vessels. The present experiments were designed to bioassay the relaxing factor(s) released by the fatty acid from endothelial cells. Femoral and brachial arteries and saphenous veins of the dog (with and without endothelium) were perfused with modified Krebs Ringer bicarbonate solution at 37°C. The perfusate was bioassayed with rings of coronary arteries without endothelium. Arachidonic acid, given to the perfusate passing through blood vessels with endothelium caused concentration-dependent relaxations of the bioassay rings. The response to arachidonic acid decreased with time. No relaxation was seen with arachidonic acid during perfusion through blood vessels without endothelium. The response to arachidonic acid was prevented by treatment of the endothelial cells with indomethacin. These experiments demonstrate that the relaxing factor liberated by arachidonic acid can be bioassayed. They suggest that it is a product of cyclooxygenase.

43.10

ANALYSIS OF DESENSITIZATION OF RESPONSES TO HISTAMINE, 5-HYDROXYTRYPTAMINE AND ACETYLCHOLINE IN CANINE TRACHEAL SMOOTH MUSCLE. S.J. Gunst, J.Q. Stropp* and N.A. Flavahan. Mayo Clinic and Fndn., Rochester, MN 55905.

Successive concentration-response curves to histamine, 5-hydroxytryptamine and acetylcholine were performed in muscle strips in vitro. A decrease in sensitivity to all three agents was observed on the second and third curves; however, the decrease in sensitivity was much more marked for histamine than for 5-hydroxytryptamine or acetylcholine. To determine whether the desensitization to histamine was due to prostaglandin release, concentration-response curves to histamine were performed on parallel muscles in the presence and absence of indomethacin ($5x10^{-6}$M). Indomethacin significantly increased the sensitivity of the muscle to histamine; however, it had no effect on the desensitization. Dissociation constants (Ka) and receptor reserve for each agent were analyzed after receptor alkylation with phenoxybenzamine. A near maximal contraction (ED95) could be achieved with only a 4.0% receptor occupancy with acetylcholine (n=6) but required a 85.6% occupancy for histamine (n=4), and a 78.3% occupancy for 5-hydroxytryptamine. Values of Ka for 5-hydroxytryptamine (n=5), histamine (n=6), and acetylcholine (n=6) were $1.8x10^{-6}$, $5.5x10^{-5}$, and $2.2x10^{-5}$, respectively. We conclude that desensitization (tachyphylaxis) to histamine cannot be attributed to prostaglandin release but may be related to an increased loss of functional receptors.

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44.1

THE MULTIPLE FORMS OF THE PHOSPHORYLATABLE MYOSIN LIGHT CHAIN IN ARTERIAL SMOOTH MUSCLE ARE NOT ARTIFACTS. M. Bárány and V. Mougios*. Dept. of Biol. Chemistry, Univ. of Illinois, Coll. of Medicine, Chicago, IL 60612

Two-dimensional gel electrophoresis of smooth muscle proteins resolves the 20-kDa myosin light chain in its phosphorylated and unphosphorylated form, and in two more minor spots. We examined whether these spots are the result of chemical modification by separating the light chain forms of porcine aorta in a cylindrical isoelectric focusing (IEF) gel and then applying it on a slab gel for a second IEF. Any spots produced artifactually in the first dimension should be produced in the second dimension too, and should appear in the final two-dimensional gel. Instead, our gels showed all spots arranged diagonally, and no additional, off-diagonal spots. Moreover, preelectrophoresis of IEF gels in the presence of the reducing agent thioglycolate, which has been reported to eliminate charge modification, had no effect on the light chain pattern. Additional evidence against artifactual modification is that the same gel electrophoretic procedure which shows four light chain spots in arterial smooth muscle, revealed only two spots in skeletal muscle, but also four spots in uterine smooth muscle. Finally, when aorta actomyosin is incubated with ATP, the two minor spots rise to levels higher than the formerly major spots. All these data show that the multiple forms of arterial myosin light chain are not experimental artifacts, but are, instead, characteristic of smooth muscle myosin. (Supported by NIH, AM-34602).

44.2

DIFFERENCES IN MYOSIN LIGHT CHAIN PHOSPHORYLATION BETWEEN ARTERIAL SMOOTH MUSCLE AND ITS ACTOMYOSIN. V. Mougios* and M. Bárány. Dept. of Biol. Chemistry, Univ. of Illinois, Coll. of Medicine, Chicago, IL 60612

Stimulation of porcine carotid arteries by KCl, norepinephrine, or stretching raises the phosphorylation level of the 20-kDa myosin light chain to 0.7 mol/mol. The light chain is mostly monophosphorylated, with a small amount (up to 8%) being diphosphorylated. The pattern is the same in homogenized aorta incubated with 1 mM ATP, 5 mM $Mg^{2+}$, and 0.1 mM $Ca^{2+}$ at low ionic strength, 25°C, and pH 7.0. Light chain phosphorylation is much higher in actomyosin prepared from aorta by extraction with 0.6 M KCl and 10 mM ATP, and reaches 1.7 mol/mol after 15 min of incubation under the above conditions. Diphosphorylation predominates in this system, and even triphosphorylation is detected. Monophosphorylated light chain contains phosphoserine, whereas di- and triphosphorylated light chain contains both phosphoserine and phosphothreonine at comparable amounts. The molar ratio of phosphoserine to phosphothreonine in total light chain is 11 in intact arteries, but only 1.3 in actomyosin. These results show that, although arterial smooth muscle contains protein kinases capable of incorporating up to 3 mol of phosphate per mol of light chain, a factor(s) exists that maintains the level of light chain phosphorylation below 1 mol/mol in intact or homogenized muscle. (Supported by NIH, AM-34602).

44.3

EFFECT OF SODIUM-PUMP INHIBITION ON CALCIUM CONTENT AND INFLUX OF RAT AORTIC SMOOTH MUSCLE. Dianne C. Kikta, Bockus Research Inst., Graduate Hosp., Phila., PA 19146.

The aim of this study was to determine the effects of sodium (Na)-pump inhibition on rat aortic intracellular calcium content ($[Ca]_i$) and influx. The thoracic aortae of 9-wk old male Wistar rats (n = 24) were divided into 6 pieces. Na-pump inhibition was achieved by exposure to either $10^{-4}$ M ouabain for 30 min (2 pieces) or potassium (K)-free physiological salt solution (PSS) for 18 hrs (2 pieces). All tissues were then exposed to their respective solutions, labelled with $^{45}Ca$ (1 $\mu$Ci/ml) for 130 min (for Ca content). During the last 10 min in $^{45}Ca$, norepinephrine (NE, $10^{-5}$ M) was added to one piece of aorta from each of the 3 groups; vehicle was added to the other. For Ca influx, $^{45}Ca$ was added during the last 1 min of NE or vehicle only. Extracellular $^{45}Ca$ was removed by washing with 2 mM EGTA-Ca-free PSS at 4°C for 45 min. Exposure to NE for 10 min significantly elevated $[Ca]_i$ and Ca influx of rat aortic smooth muscle. Ouabain prevented the NE-induced increase in $[Ca]_i$ but, with or without NE, elevated significantly Ca influx rate. On the other hand, K-free PSS elevated significantly $[Ca]_i$, with or without NE, but had no effect on Ca influx rate and prevented the NE-induced increase in Ca influx. The ouabain effects may be non-Na-pump related. Thus, Na-pump inhibition may increase rat aortic $[Ca]_i$, possibly due to a decrease in Ca efflux. (Supported by NIH Grants HL33416 & RR05874-07.)

44.4

APAMIN BLOCKS SEROTONIN-STIMULATED $^{86}Rb$ EFFLUX IN PIG CORONARY ARTERIES. Robert H. Cox, Bockus Research Institute, Graduate Hospital; Department of Physiology, University of Pennsylvania, Phila., PA 19146.

Ring segments of right coronary artery 10 cm distal to its origin were obtained from pig hearts. Segments were $K^+$-depleted by overnight cold storage in $K^+$-free Krebs. The segments were loaded with $^{86}Rb^+$ in normal Krebs for 4 hours at 37°C. The samples were passed sequentially through a series of tubes at 10 or 20 minute intervals. The activity in the samples and tubes were added in reverse order to determine efflux curves and efflux rate constants determined. Serotonin stimulated the rate constant for $^{86}Rb^+$ efflux from 3.2 $\pm$ 0.2 to 4.2 $\pm$ 0.6 ($10^{-3}$ $min^{-1}$). Apamin (1 $\mu$M) added 20 minutes prior to serotonin exposure completely blocked the serotonin-activated increase in $^{86}Rb^+$ efflux. Apamin by itself had no effect on efflux in the absence of activation. No significant changes in efflux rate constant over the same time course were found in unstimulated samples. Apamin is thought to be a specific $Ca^{2+}$-activated $K^+$ channel blocker. These results suggest that serotonin activated $Ca^{2+}$-dependent $K^+$ channels and that apamin selectively blocks this increase. (Supported by HL-28476 and AHA.)

44.5

CALCIUM INFLUX STUDIES IN RABBIT AORTIC SMOOTH MUSCLE CELLS IN CULTURE. Debra Forman* and Tom Tulenko. The Medical College of Penna., Philadelphia, Pa. 19129

The object of this study was to assess the time dependent nature of basal and $K^+$ activated calcium influx into arterial smooth muscle cell (SMC) monolayers grown from rabbit aorta. Triplicate cell cultures for each time point tested were plated at a density of 350+/-5 cells/$mm^2$ and grown to confluence in MEM supplemented with 10% FBS. All cultures were under the 18th passage at the time of analysis. Prior to assay, the cultures were washed free of MEM and equilibrated for 30 minutes at 37°C in either normal HEPES buffered solution (HBS) +/- 0.1uM verapamil, or high KCl (80mM substituted for NaCl) HBS +/- 0.1 uM verapamil. Each culture was incubated with $^{45}Ca$ (1uCi/ml) and terminated at various intervals by rinsing with iced HBS solution. Basal calcium uptake for 10 minutes was 0.151 nm/mg protein/min and was not affected by verapamil. $K^+$ depolarized cells demonstrated an initial steep rise in calcium (26.7 nm/mg protein/min) which peaked at 15 seconds, and a much slower accumulation (0.107 nm/mg protein/min) which continued for 10 minutes, similar to that observed during basal accumulation. Verapamil produced a marked attenuation of the initial steep rise in calcium in depolarized cells resulting in an uptake rate similar to basal uptake. In comparison to studies in rings of rabbit aorta, the fast component of calcium influx into depolarized SMC monolayers saturates within 15 seconds compared to several minutes typically observed in intact rings, reflecting a fundamental difference between calcium influx in SMC monolayers and SMC in the intact arterial wall. (Supported in part by NIH grants HL30496, HL07443 & AG04908)

44.6

HEALING-OVER IN SMOOTH MUSCLE. Nadya Fernández* and Walmor C. De Mello. Department of Pharmacology, Medical Sciences Campus, UPR, San Juan, Puerto Rico 00936.

The establishment of a high resistance barrier near lesion is well documented in heart muscle. This process of healing is related to the diffusion of Ca ions through the cut-end and the consequent increment of junctional resistance (De Mello, 1972). In the present work the existance of a similar phenomenon was investigated in guinea-pig taenia coli which has cable properties (Tomita, 1967). In muscles immersed in normal Tyrode solution the depolarization and the fall in input resistance caused by lesion were quickly reversed. The values of input resistance (1 MΩ) measured 20 min after damage showed increasing values toward the cut-end. In Ca-free solution healing-over was also found. Experiments performed with Ca-free solution containing La (2 mM) or exposing the tissues to high K solution (60 mM) for 10 min, abolished the ability of the muscle to heal-over in Ca-free solution. The results suggest that Ca from intracellular or membrane stores promotes healing-over in smooth muscle. (Supported by Grant No. HL 34353 from NIH.)

44.7

EXTRACELLULAR CALCIUM-DEPENDENT MEMBRANE DEPOLARIZATION IN CEREBROVASCULAR SMOOTH MUSCLE. Takao Bun, Shigeru Nishizawa, and John W. Peterson. Massachusetts General Hospital, Boston, Massachusetts 02114

The effects of changes in extracellular [$Ca^{++}$] on the membrane potential of vascular smooth muscle cells in isolated, perfused segments of canine basilar artery was studied. As $[Ca^{++}]_o$ decreased from 2.5 to 0 mM at constant intraluminal pressure of 120 mm Hg, $E_m$ depolarized progressively from about -45 to -20 mV. While $E_m$ shows a dependence on pressure at normal $[Ca^{++}]_o$, the $Ca^{++}$-dependent depolarized $E_m$ is independent of pressure. Our attempts to identify what ion flux is responsible for the $Ca^{++}$-dependent depolarization are inconclusive. The ion flux is apparently not through $Ca^{++}$ or $Na^+$ channels since verapamil had no effect on $E_m$ and amyloride only slightly repolarized the $Ca^{++}$-free tissue. An increased $Na^+$ influx in the absence of $Ca^{++}$ is not likely, since $Na^+$- and $Ca^{++}$-free medium only slightly repolarized the tissue. In the presence of $Ca^{++}$, $Na^+$-free medium had no effect on $E_m$, but caused the vessel to constrict somewhat. Our findings indicate that $Na^+$ and $Ca^{++}$ may compete for entry into the cell and that extracellular [$Ca^{++}$] may have an important effect on $K^+$ and $Cl^-$ conductances which can alter smooth muscle cell membrane potential.

44.8

EFFECT OF HEMODYNAMIC STRESS ON MEMBRANE POTENTIAL OF VASCULAR SMOOTH MUSCLE CELLS IN VIVO AND IN VITRO. E. Monos, S. Contney*, A. W. Cowley, Jr., W. J. Stekiel. Dept. of Physiol., Med. Coll. of Wis., Milwaukee, WI 53226

To elucidate the mechanisms leading to the alterations of the vascular wall observed with exposure to mechanical overload, techniques were developed to vary the hemodynamic stress while smooth muscle membrane potentials ($E_m$) were measured. In vivo shunts with controllable pressure and flow were established between the femoral artery and saphenous vein of rats. In vitro, segments of this vein were perfused with PSS using a variable outflow resistor. $E_m$ measurements were made with glass microelectrodes. Mechanical properties of the segments were determined for 5 mmHg pressure increments. Opening the A-V shunt resulted in an immediate 12.1±0.9 mV depolarization of the cell membrane which was sustained for the 1-hour test period (control $E_m$:-51.2±0.6 mV). Return of pressure and flow to pre-shunt values resulted in normalization of the $E_m$ values. In vitro, setting the pressure just above the steep part of the pressure vs. diameter curve (15.0±0.8 mmHg; 18-20x $10^4$ dyne/$cm^2$ tangential stress) without altering the volume flow in the vein, resulted in a 18.6±0.9 mV depolarization during the 1-1.5 hour observation period (control $E_m$:-53.1 ± 1.7 mV). It is concluded that a one-hour hemodynamic stress causes a sustained, reversible depolarization of the venous smooth muscle both in vivo and in vitro. The chemical composition of the arterial blood does not contribute to the effect. Supp. NIH HL 2 9587.

44.9

ARTERIAL WALL Na CONTENT IN THE RENAL HYPERTENSIVE DOG. D.M. Moisey, R.H. Cox, R.J. Bagshaw, Phila. Coll. Osteo. Med.; Bockus Res. Inst., Graduate Hosp.; and Univ. of Penna., Philadelphia, PA 19146.

The present study examines Na translocation in carotid arteries (CA) from control, renal hypertensive and "resolved" hypertensive dogs. Cell Na content was determined in steady-state and Na-loaded arteries at 0°C using a lithium (Li) substitution technique and atomic absorption spectroscopy. No difference in exchangeable cell Na was seen in steady-state CA among the groups (24 mmol/kg). However, differences were seen in Na-loaded CA. Hypertensive CA exchanged Li for Na faster, resulting in a lower cell Na content (45 mmol/kg) compared to CA from the resolved (75 mmol/kg) or control groups (100 mmol/kg). Treatment of CA from control or resolved animals with ouabain, dihydroouabain, or furosemide did not influence cell Na content. However, both ouabain and dihydroouabain prevented Na loss from the hypertensive artery, resulting in cell Na contents similar to those seen in CA from the resolved hypertensives. In addition, monensin decreased cell Na content in the hypertensive and resolved groups. These data suggest that (1) CA from renal hypertensive dogs are leaky to Na, (2) agents which interfere with Na translocation reverse this condition, and (3) resolution of the renal hypertension results in partial recovery of cell Na content and related ionic mechanisms. (Supported by HL28476 and HL33704.)

44.10

ALTERED SMOOTH MUSCLE RESPONSES TO TUMOR GROWTH. E.A. LENTINI J.G. BASSETT*, J. MOBINI*AND K. NAKHGEVANY*. Depts. of Surgery and Pathology, Medical College of Pennsylvania, Philadelphia, PA. 19129.

The effects of a distal tumor on the host blood vessel dynamics has been examined, in vitro, by using a previously developed rat tumor-vessel model. (Physiologist 28:327, 1985). Results have shown that the isometric developed tension ($F/cm^2$) as revealed by dose response experiments of tumor host (TH) aortic rings was less than that of corresponding rings from control subjects ($P<.05$). The attenuated vasoconstriction was obtained using K+ or norepinephrine (NE) as the agonist. The $ED_{50}$ was unaltered. Analysis of the NE contraction curves revealed a significant difference in the fast component ($P<.05$). The slow components were statistically similar. Passive distensions to 150% equilibrium length revealed comparable values for the modulus of elasticity $1 \times 10^{-6}$ dyn/$cm^2$. Results were reproducible in animals with transplanted tumors developed from the original chemically induced primary tumor. Tumors were transformed from epithelial to sarcomatoid characteristics during successive transplants. Currently, histopathologic features have not been quantitatively correlated with the developed tension. Present studies indicate that a distal tumor exerts its depressing effect on the blood vessel through the fast component of the contraction curve.

(Supported by R. J. Reynolds)

44.11

In-Vitro Effects of Muscarinic and Adrenoceptor Agonists and Antagonists on Intestinal Segments from Monodelphis domestica. William P. Ventura. Biology Dept. Pace University. Pleasantville, N. Y. 10570

Intestinal segments from M. domestica were used to record in-vitro spontaneous motility and responses to Acetylcholine, Norepinephrine, Pindolol, Propranolol, Timolol Maleate and Atropine.

Control data indicates that all intestinal segments exhibited a regular and consistent pattern of spontaneous motility for up to 5 hrs. The average force of contraction response was 4.85±0.17 grams and frequency of contraction response was 33.71±3.12 contractions per 20 minute period. Force declined by 8% and frequency by 13% over the 5 hr. control experiments. All drugs tested in several dose ranges. All doses in micrograms/ml bath.

| DRUG | DOSE RANGE | FORCE | FREQUENCY |
|---|---|---|---|
| Acetylcholine | (0.00001-1) | up | down |
| Norepinephrine | (0.00001-1) | down | up |
| Timolol Maleate | (0.0125-2) | down | up |
| Propranolol | (0.0125-2) | down | up |
| Pindolol | (0.0125-2) | down | up |
| Atropine | (0.001-10) | down | up |
| Acetylcholine (0.1 or 1) after Atropine (.0001-10) | | down | up |
| Norepinephrine (0.1 or 1 after Timolol or Propranolol | | up | down |

47.1

BURN INDUCED CHANGES IN ACETYLCHOLINE RECEPTORS(ACR) IN THE DIAPHRAGM. Chungsook. Kim*, Nobuo. Fuke*, and J.A.J. Martyn* (Spon:J.F.Tomera). Dept. of Anaesthesiology, Harvard Medical School, Mass. General Hospital, and Shriners Burns Institute, Boston, MA 02114.

Burned patients have altered response to d-Tubucurarine (dTC). Changes in ACR in diaphragm was assayed to examine systemic effects of burn. Response to dTC was also measured at gastrocnemius during stimuli to sciatic nerve. The experiments were followed NIH guidelines. Spleen of male SD rats was removed 10 days before burn. Cumulative i.v. doses or .1 mg/kg i.v. bolus were given. The ACR number was estimated using $^{125}$I alpha-bungarotoxin method. Although 50% burn was inflicted the size of burn on experimental days had decreased to 20-30% of body surface. The $ED_{50}$ of dTC at 14 days postburn were not significantly different from the control. However the amount of ACR in burn diaphragm(8.87±2.18 fmole/μg protein, n=10) was higher than that in control(5.10±1.44, n=14)(p<.001). In the bolus study the effect of dTC at 14 and 28 days were not significantly different from the control. The number of ACR was increased significantly about 2 fold at 14 days postburn but returned to control level at 28 days postburn. The effect of .1 mg/kg dTC was significantly correlated to the loss of body weight after burn($r^2$=.6, p<.003). Similar to disuse atrophy and denervation burn induces an increase in ACR. The reason ACR increases following burn is still unknown. (Supported in part by NIH grant GM31569 and the Shriners Burns Institute)

47.2

INCREASES IN BURN SIZE AND RESULTING CHANGES AT THE NEUROMUSCULAR JUNCTION (NMJ) IN MICE. JOHN F. TOMERA AND J.A.J. MARTYN*. Dept. Anaesthesiology, Harvard Medical School, and Anesthesia Services, Massachusetts General Hospital and Shriners Burns Institute, Boston, MA 02114.

The purpose of this study was to evaluate changes at the NMJ induced from burn trauma of 20, 30, and 50% total surface area burn in mice. This study presents data gathered at Day 21 post-burn. Male $CF_1$ mice were used for all analyses. Animals were givern a full-thickness scald burn with water at 95°C for 8 sec while under anesthesia. Analyses performed on the gastrocnemius muscle, during electrical stimulation evaluated changes at the acetylcholine (ACH) receptor through d-tubocurare (dTC) dose-respone curves and induced changes in cyclic nucleotide levels. By Day 21 post-burn there was observed a 2-fold increase (P<.002) for $ED_{50}$ values (mg/kg) based on dTC inhibition of contraction for mice subjected to 30% (.08±.03, N=5) and 50% (.10±.04, N=6) burn compared to controls (.04±.01, N=5). Adenosine 3':5' cyclic monophosphate (cAMP) and guanosine 3':5' cyclic monophosphate (cGMP) levels (pmol/mg prot) were measured by $^{125}$I-radioimmunoassay. Levels of cAMP were increased (P<.05) for the 30% (19.42±1.99) and 50% (23.62±6.21) group compared to controls (10.81±2.19). No change was observed in cGMP levels. However, the cAMP/cGMP ratio was increased (P<.0001) 3-fold for the 50% group. Our observations add new findings for trauma evoked by 20, 30, and 50% burn size in the murine model. (Supported in part by NIH Grant GM31569 and the Shriners Burns Institute)

47.3

EFFECTS OF ANTIDROMIC STIMULATION OF THE VENTRAL ROOT ON GLUCOSE UTILIZATION IN THE VENTRAL HORN OF THE SPINAL CORD. M. Kadekaro, W.H. Vance,* M.L. Terrell,* and H.M. Eisenberg.* Division of Neurosurgery, The University of Texas Medical Branch, Galveston, TX 77550.

We have shown (PNAS 82:6010, 1985) that axon terminals in the dorsal horn of the spinal cord but not the soma in the dorsal root ganglion are the sites of enhanced metabolic activity during activation of the sciatic nerve. To determine in another system whether the soma could enhance their rates of glucose utilization in response to increased activity, the ventral root and ventral horn of the spinal cord were chosen as a model. The [$^{14}$C]deoxyglucose method was used. Adult Sprague-Dawley rats were anesthetized with urethane, paralyzed and artificially ventilated. Laminectomy was performed at L3-L5 and the dorsal and ventral roots at L5 were isolated and sectioned on both sides. Two pairs of silver electrodes were positioned on one ventral root, the distal one for stimulating and the proximal one for recording the compound action potential. Antidromic stimulation of the ventral root with pulses of 0.2 ms, frequencies of 30-90 Hz and intensities of current of 10-100 μA did not change glucose utilization on the stimulated side. These results confirm that the soma do not increase their rate of glucose utilization in response to increased electrical activity.

47.4

PHYSIOLOGY OF SWEET TASTE PERCEPTION IN MAN. J.H. Shah. V.A. Hospital and University of Missouri, Columbia, MO. 65201

The threshold and acuity of sweet taste perception were evaluated in healthy normal volunteers (22 males and 23 females of similar ages) and 15 adult diabetic patients. The test for sweet taste perception was done by a forced choice triangle method utilizing distilled water and different concentrations of dextrose solutions (.001 M to .3 M). In normal males the threshold (.04±.005 M) and acuity (.06±.01 M) for sweet taste occurred at significantly lower concentrations of dextrose solutions than those observed (threshold = .07±.01 M, acuity = .08±.01 M) in the normal females. The ability to perceive sweet taste did not change significantly when above tests were repeated in several subjects after an overnight fast or 2 to 3 hours after meals. Similarly a comparison of threshold and acuity for sweet taste in age matched obese and non-obese subjects showed no differences. Although a tendency towards deterioration for sweet taste perception was observed with increasing age, these differences were not significant. In diabetic patients the threshold (.09±.01 M) and acuity (.12±.01 M) for sweet taste were significantly impaired than those observed in the normal subjects. Conclusions: 1) The males perceive sweet taste at lower dextrose concentration than females, 2) aging shows a tendency towards deterioration in sweet taste perception, 3) the obese, fasting or postprandial state does not affect sweet taste, and 4) the sweet taste perception is significantly altered in adult diabetic patients.

47.5

FIBROBLASTS FROM ALZHEIMER VICTIMS TRANSPORT CHOLINE SLOWER THAN DO NORMAL FIBROBLASTS. L. C. Mokrasch, LSU Medical Ctr., New Orleans, La. 70119.

Disturbances in cholinergic processes are imputed as causes of the neuropathology of Alzheimer's disease. To test whether defects in the transport of acetylcholine precursors exist and whether the transport defects are expressed in fibroblasts from Alzheimer victims this study was begun. 3 lines of Alzheimer cells and 3 lines of age- and sex-matched normals were grown in culture. Choline and serine are transported into normal cells with pseudo-zero order kinetics for about 20 and 200 minutes, respectively; Alzheimer cells transport these compounds linearly with time for slightly shorter periods. Influx kinetic analysis revealed that most cells had 2 sets of Km's and Vmax's for choline.Normals had values averaging 0.54 mM and 0.21 uMol/hr/mg for the higher Km and Vmax; the corresponding values for the Alzheimer cells were 0.43 mM and 0.09 uMol/hr/mg. For the lower set of Km's and Vmax's, the normals' values were 0.038 mM and 13 nMol/hr/mg and the Alzheimers values were 0.087 mM and 7.9 nMol/hr/mg. Both to the normal cells and to the Alzheimer cells, $Na^+$ was inhibitory to choline influx to about the same degree, rather than being stimulatory. Hemicholinium-3 inhibited choline influx in both cells to a similar degree. The transport of choline into fibroblasts exhibits some of the characteristics of its transport into neural tissue and the influx is slower into Alzheimer cells than into normals.

47.6

ATRIAL NATRIURETIC FACTOR (ANF) STIMULATES CYCLIC GMP ACCUMULATION IN SELECTED REGIONS OF RAT BRAIN.
R.R. Fiscus, B.T. Robles* and F. Murad*. Dept. Physiol., Loyola Univ. Med. Ctr., Maywood, IL 60153; Dept. Med. & Pharmacol., Stanford Univ. VA Med. Ctr., Palo Alto, CA 94304.

Previous studies from our laboratory have shown that ANF selectively activates particulate, but not soluble, guanylate cyclase in certain rat tissues and that one class of ANF receptor from rat lung appears to be the same glycoprotein as particulate guanylate cyclase. We have also found that C6-2B rat glioma and PC-12 rat pheochromocytoma cells, which possess high levels of particulate guanylate cyclase, respond to ANFs with increased accumulation and efflux of cyclic GMP. Since these cyclic GMP responses may be unique to transformed cell lines, we also investigated the effects of ANF in normal brain tissue. Rat brains were rapidly removed, placed in oxygenated PSS and dissected into 6 regions: hypothalamus (HT), cerebral hemispheres (CH), hippocampus (HP), corpus striatum (CS), cerebellum (CB), and the remainder, brain stem (BS). The ANF atriopeptin II (100 nM) elevated cyclic GMP 2- to 24- fold in all brain regions except CB. The lack of response in CB may be related to the high basal levels of cyclic GMP that could mask responses to ANF. The data indicate that normal neural tissue from various regions of rat brain respond to ANF with increases in cyclic GMP levels. The data support our proposal that cyclic GMP may serve as a mediator of ANF actions in neural tissue. Supported by NIH (HL28474, AM30783), Veterans Admin. and Council for Tobacco Res., U.S.A.

47.7

CHARACTERIZATION OF $\alpha_2$-ADRENERGIC RECEPTORS IN RAT NEURONAL AND GLIAL CELL CULTURES. Elaine M. Richards*, Mohan K. Raizada, M. Ian Phillips and Colin Sumners. University of Florida, Gainesville, Florida 32610.

In order to determine whether $\alpha_2$-adrenergic receptors exist in neuronal and glial cell cultures, the binding was characterized using $^3$H-Yohimbine as the ligand. Neuronal- and glial-enriched cell cultures were prepared from one-day-old rat brains. Both neurons and glia displayed specific $^3$H-Yohimbine binding that was reversible, time-dependent, linear with respect to protein content, and in neuronal culture, saturable. In neurons and glia the potency series of rauwolscine = yohimbine >> clonidine > prazosin > corynanthine = propranolol = naphazoline = phenylephrine = norepinephrine was observed, suggesting specific $\alpha_2$-adrenergic binding. In neurons, kinetic analysis revealed an apparent $K_D$ of 1.69 ± 0.42 nM, n = 3. Scatchard analysis revealed a $K_D$ of 9.6 ± 2.9 nM, n = 4, and a $B_{max}$ of 79.8 ± 11.1 fmoles/mg protein, n = 4. In glia, preliminary experiments showed two binding sites: one of high affinity and low capacity and the other of low affinity and high capacity. In conclusion, this is the first demonstration that $\alpha_2$-adrenergic receptors exist in both neurons and in glia. (Supported by NIH grants NS-19441, HL-33610 and HL-27334.)

47.8

EFFECT OF ACUTE ADMINISTRATION OF BROMOCRIPTINE AND YOHIMBINE ON PHARMACOLOGICALLY-INDUCED DRINKING IN ESTROGEN-TREATED RATS. Melvin J. Fregly. Dept. Physiol., Univ. of Florida, Col. Med., Gainesville, FL.

Chronic administration of an estrogenic agent attenuates the drinking response of rats to treatment with a variety of dipsogenic agents, including isoproterenol (ISO) and angiotensin II (AII), and increases plasma concentration of prolactin (PRL). Treatment with PRL is also known to reduce the drinking response to administration of ISO. Hence, a possibility existed that the antidipsogenic effect of chronic treatment with estrogen (E) was mediated by the increased plasma PRL concentration. Since bromocriptine (BROM), a dopaminergic agonist, is known to reduce plasma PRL concentration in E-treated rats, it was administered (1.0 mg/kg, i.p.) 15 min prior to treatment with either ISO (25 ug/kg, s.c.) or AII (200 ug/kg, s.c.). Other groups were administered ISO or AII alone. Water intakes were measured at 0.5, 1.0 and 2.0 hr thereafter. The antidipsogenic effect of chronic treatment with estradiol benzoate (EB) (30.4 and 45.7 ug/kg/day) can be reversed, at least partially, by acute administration of BROM. As with E treatment, acute administration of clonidine, an alpha$_2$-adrenoceptor agonist, is known to attenuate the drinking response to a variety of dipsogenic agents. Administration of the alpha$_2$-adrenoceptor antagonist, yohimbine, increased significantly the AII-induced water intake of control rats but failed to affect that of EB-treated rats. (Supported by HL14526 from NHLBI).

47.9

**EFFECTS OF 5-HT REUPTAKE INHIBITION ON REFLEX BEHAVIORS IN MATURING MICE.** **Cecilie Goodrich and Rose Chermansky*. Cleveland State Univ., Cleveland, OH 44115**

**Citalopram (Pfizer), a selective inhibitor of the 5-HT reuptake mechanism, may be expected to produce effects by prolonging the exposure of postsynaptic 5-HT receptors to physiologically released 5-HT. Previous studies on thermoregulation in this laboratory have yielded results consistent with such an effect, including a possibility of inducing precocious maturation under certain conditions. Since 5-HT neurons are known to innervate the ventral horn of the spinal cord and motor areas of the cerebral cortex, possible effects of a single dose of citalopram (20 mg/kg IP) were investigated 24 hr later. Normal patterns of maturation were established for our mice in a battery of 14 behaviors similar to those reported by Wahlsten (1974). Six behaviors which mature during the first or second postnatal week were studied "double blind" in 6 litters with vehicle-injected littermate controls. Vertical climbing on a screen, hindlimb grasp, a "propeller" balancing movement of the tail, and auditory startle were all significantly enhanced. Small, nonsignificant changes were seen in the "popcorn" startle and ear twitch responses. These effects were found only during the period of maturation for a particular response.** **(Supported by a grant from the National Institute of Neurological and Communicative Disorders and Stroke.)**

47.10

MOTOR IMPAIRMENT AFTER $\Delta^9$-TETRAHYDROCANNABINOL INTAKE IN RATS: EFFECT OF OTHER CANNABINOIDS. Michael Kogan* and George Alexander, Neurotoxicology Unit, NY State Psychiatric Inst., New York, NY 10032.

Neuronal control of motor coordination is impaired by marijuana. The principal active ingredient in marijuana is $\Delta^9$-tetrahydrocannabinol (THC). However human THC blood levels, although proportional to the THC content in smoked marijuana, have not been shown to correlate with degree of motor impairment. It seems that additional smoke components, such as cannabinol (CBN) and cannabidiol (CBD), largely inactive in themselves, modify the THC effect. We injected rats i.v. with pure THC, pure CBN or a mixture of THC and CBN, 5:1 (ratio comparable to that in an authentic marijuana sample) and measured motor impairment on a rotorod treadmill. CBN alone had no effect; THC decreased motor coordination 42% below baseline. The THC effect reached its peak between 30-40 min, then waned rapidly. The effect of the mixture of THC and CBN was 30% less pronounced at peak time but persisted for at least 4-5 hrs. All THC-treated rats recovered completely 3 hrs after injection, while the group receiving the THC and CBN mixture showed only a 50% recovery. Thus, presence of CBN attenuated THC activity while extending its duration.

47.11

ALTERED MATERNAL BEHAVIOR IN RATS TREATED WITH LITHIUM. George J. Alexander, Jeri A. Sechzer and Kenneth W. Lieberman. NY State Psychiatric Inst., NY, NY 10032; NY Hosp.-Cornell Univ. Med. Ctr., White Plains, NY 10605; Catholic Med. Ctr. Jamaica, NY 11432

Ingestion of lithium (Li) by manic-depressive patients during pregnancy raises questions about its effect on the behavior of the mother. Although animal studies have shown Li to be harmful in a variety of animal forms from ciliates and sponges to amphibians, birds and rodents, little attention has been given to the effects of Li on behavior of the mother with her offspring if she has ingested Li during gestation and/or the neonatal period. To explore this question, we treated female Sprague-Dawley rats with daily doses of Li salts. Li treatment was continued during gestation and lactation. Maternal behavior was markedly altered. Nest-building and self-grooming by treated dams was absent. Nursing, grooming of pups was minimal and of short duration. Cannibalization of ill pups did not occur. This aberrant pattern persisted throughout the first 2-3 postpartum weeks. Development of early maternal behavior appears dependent upon hormonal changes, involving prolactin in conjunction with the steroids, estradiol and progesterone. Li may interfere with hormonal regulatory mechanisms during the development of maternal responsiveness.

48.1

$O_2$ DELIVERY TO CONTRACTING MUSCLE DURING HYPOXIC OR CARBON MONOXIDE HYPOXIA. C.E. King, S.L. Dodd, and S.M. Cain, University of Alabama at Birmingham, 35294.

The contracting canine gastrocnemius muscle preparation was used to investigate the mechanism used by this tissue to offset a decreased $O_2$ supply during two forms of hypoxia; hypoxic hypoxia (HH) (n=6) and carbon monoxide hypoxia (COH) (n=6). Muscle $O_2$ uptake, blood flow, $O_2$ extraction, and developed tension were measured at rest and at 1 twitch/sec isometric contractions in normoxia and in hypoxia. At rest and contractions in normoxia and at rest in hypoxia, no differences were observed between the two groups. During contractions and hypoxia, however, $O_2$ uptake decreased ($p<0.05$) in the COH group but not in the HH group. Tension development fell ($p<0.05$) by 10 min of hypoxia in the COH group and was lower than that observed in the HH group throughout 30 min of hypoxia. Blood flow increased in both groups during hypoxia, but more so in the COH group. $O_2$ extraction increased ($p<0.05$) during contractions in the HH group but fell ($p<0.05$) in the COH group. The $O_2$ uptake limitation during COH and contractions was associated with a lesser $O_2$ extraction. Examination of $P_{50}$ values indicated that the leftward shift in the oxyhemoglobin dissociation curve during COH was primarily responsible for the reduction in $O_2$ extraction, however, direct tissue effects of carbon monoxide could not be entirely ruled out. (Supported by NIH Grants HL-14693, HL-26927 and the Canadian Heart Foundation.)

48.2

DILUENT BOLUS WASHOUT FROM CANINE HINDLIMB FOLLOWING DNP AND HYPOXIA. S.M. Cain, W.E. Bradley*, C.R. Katholi*, and C.K. Chapler. Univ. of Alabama at Birmingham, 35294, and Queen's Univ. Kingston, Ont. K7L 3N6.

Perfusion heterogeneity is a feature of resting canine skeletal muscle that we found earlier to increase with onset of severe hypoxia. We next asked whether increased $O_2$ demand would decrease perfusion heterogeneity and prevent any further increase with hypoxia. Sufficient 2,4-dinitrophenol (DNP) was injected in 8 anesthetized dogs to increase total $O_2$ uptake about 2.5x and limb skeletal muscle $O_2$ uptake about 4x. Limb blood flow increased about 60% and $O_2$ extraction more than doubled. Perfusion heterogeneity was quantified by the wash-in of a 2.5 ml bolus of saline so that the hematocrit change in the venous outflow described a curve that was the envelope containing the red cell transit times through the limb. A coefficient of skewness was derived from a fitting function (cubic spline fit) that increased with increasing heterogeneity. This decreased with DNP. Contrary to behavior in non-stimulated skeletal muscle, flow increased with hypoxia ($F_IO_2 = 0.09$) and perfusion heterogeneity did not increase. Increased $O_2$ demand was apparently a more effective regulator of microcirculation in skeletal muscle than was a severely decreased $O_2$ supply. (Supported by NIH Grant HL 14693 and a grant from MRC of Canada.)

48.3

THE EFFECT OF SYMPATHETIC STIMULATION ON HINDLIMB BLOOD FLOW IN ANEMIA. P. Kubes*, C.K. Chapler and S.M. Cain. Depts. of Physiology, Queen's University, Kingston, Ontario, K7L 3N6 and University of Alabama in Birmingham, USA 35294.

The effect of sympathetic stimulation on hindlimb blood flow was studied in 8 anesthetized, paralyzed and ventilated dogs prior to and during acute anemia. The left sciatic nerve was doubly ligated and transected; the distal end was stimulated at a supramaximal voltage (freq=12, dur=1.5 ms) for 4 min at normal hematocrit (Hct) and again at 30 min of anemia induced by an isovolemic dextran-for-blood exchange. Values for limb blood flow ($\dot{Q}_L$) and arterial blood pressure were obtained before and during nerve stimulation; resistance and vascular hindrance were determined for the same time periods. Nerve stimulation produced a decrease in $\dot{Q}_L$ ($p < 0.01$) at both normal Hct (116 to 51 ml/kg/min) and during anemia (154 to 86 ml/kg/min). The minimum value (51 ml/kg/min) observed prior to anemia was significantly less than that during hemodilution (86 ml/kg/min). Hindlimb resistance during nerve stimulation was greater ($p < 0.01$) at normal Hct (2.66 PRU) than during anemia (1.26 PRU) but there was no difference in vascular hindrance between the two conditions. These data demonstrate that the reduction in viscosity during anemia can limit redistribution of periperal blood flow resulting from sympathetic nerve stimulation.
(Supported by the MRC of Canada and NHLBI, 14693).

48.4

EFFECTS OF POLYCYTHEMIA ON TOTAL AND REGIONAL OXYGEN DELIVERY, UPTAKE AND HEMODYNAMICS. R.L. Stork*, S. L. Dodd, S.M. Cain, and C.K. Chapler. Univ. of Alabama at Birmingham 35294, and Queen's Univ., Kingston, Ont. K7L 3N6.

Polycythemia raises oxygen carrying capacity but increases viscosity so that systemic oxygen delivery is decreased. We have examined two regional responses to these consequences. After a 20 minute normocythemic control, hematocrit was increased isovolemically from 42 to 65% in 8 anesthetized, dogs with donor erythrocytes. Changes in hindlimb skeletal muscle (leg) and intestinal (gut) $O_2$ uptake ($\dot{V}O_2$), $O_2$ delivery ($\dot{D}O_2$), $O_2$ extraction ratio (ER), blood flow ($\dot{Q}$) and vascular resistance (R) were followed for 100 minutes and compared to the whole body (WB) responses. Polycythemia significantly increased R generally but the change in gut R was significantly greater than in WB or leg. As a result, leg $\dot{Q}$ fell least and leg $\dot{D}O_2$ was better preserved than in gut or WB. ER was significantly higher in leg and gut than WB. $\dot{V}O_2$ was maintained at the normocythemic level in both gut and WB but increased in the leg. Although resting skeletal muscle had a lower $\dot{V}O_2$ than WB or gut, it maintained blood flow and $O_2$ extraction better than either when cardiac output was decreased by polycythemia. (Supported by NIH Grant HL 14693, USAFSAM Contr. 7930-14-6C, and a grant from MRC, Canada.)

48.5

MECHANISM OF AUGMENTED ENDOTHELIUM-DEPENDENT RELAXATIONS TO ACETYLCHOLINE IN FISTULA-OPERATED CANINE ARTERIES. V.M. Miller and P.M. Vanhoutte, Department of Physiology and Biophysics, Mayo Clinic, Rochester, MN 55905.

Creation of a fistula between the femoral artery and vein of the dog results in a three-fold increase in blood flow in the artery proximal to the fistula. In these arteries, the endothelium-dependent, relaxation-response curve to acetylcholine is shifted to the left of that from sham-operated arteries. A bioassay system was used to determine whether the augmented relaxations are due to altered release of, or a changed sensitivity of the smooth muscle to endothelium-derived relaxing factor(s). Rings of femoral artery without endothelium, taken from unoperated vessels, were superfused with solution which passed through the lumen of either fistula- or sham-operated arteries (with endothelium). Relaxations initiated by acetylcholine and the calcium ionophore A23187 were greater in arteries superfused with solution from fistula-operated vessels. In the reverse experiment, rings of fistula- and sham-operated arteries without endothelium were superfused with solution which passed through the luman of unoperated arteries (with endothelium). Relaxations initiated by acetylcholine, A23187 and nitroglycerine were the same in fistula- and sham-operated arteries. These data suggest that increased blood flow augments the production and release of endothelium-derived relaxing factor(s) while the sensitivity of smooth muscle to such factor(s) is unchanged.

48.6

INTRALYMPHATIC ADMINISTRATION OF PROSTAGLANDIN $F_{2\alpha}$ CONSTRICTS PRENODAL LYMPHATIC VESSELS IN THE CANINE FORELIMB. David E. Dobbins, Molly J. Buehn*, and Joe M. Dabney. Dept. Physiology, Uniformed Services University, Bethesda, MD 20814-4799.

We have previously reported that the intralymphatic administration of a number of vasoactive agents constricts prenodal lymphatic vessels in the canine forelimb. The current study was undertaken to assess the actions of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on lymphatic smooth muscle. A prenodal lymphatic vessel on the dorsal surface of the paw (n=7) was perfused at constant flow (0.034 ml/min.) with either control perfusate or perfusate containing $8.5x10^{-7}$, $8.5x10^{-6}$ or $8.5x10^{-5}$M $PGF_{2\alpha}$ for 15 minutes at each dosage. Between the sequentially increasing dosages of $PGF_{2\alpha}$, the lymphatic vessels were perfused with control lymph until lymphatic perfusion pressure had returned to control levels. Lymphatic perfusion pressure averaged 6 mmHg prior to $PGF_{2\alpha}$ administration and was not significantly altered by the lowest dosage of $PGF_{2\alpha}$. However, the two higher dosages of $PGF_{2\alpha}$ significantly increased lymphatic perfusion pressure to 11 mmHg and 16 mmHg respectively. No significant changes were seen in systemic pressure, heart rate, central venous pressure or skin small vein pressures. Forelimb arterial pressures were slightly increased at the two highest dosages. These data indicate that the intralymphatic administration of $PGF_{2\alpha}$ results in lymphatic constriction and that the threshold dosage for this constriction lies between $8.5x10^{-7}$ and $8.5x10^{-6}$M.

48.7

STOCHASTIC ASPECTS OF LEUKOCYTE TRANSIT IN ARTERIOLES.
Robert Mayrovitz*, Ran Rubin* and Harvey N. Mayrovitz
Miami Heart Institute, Miami Beach, FL 33140

Circulating leukocytes that become entrapped within the microvasculature affect the outcome of several pathological states including myocardial infarction. However, no quantitative data describing the stochastic features of leukocyte delivery to capillaries is available for any conditions. Thus we studied leukocyte transit through arterioles (diameter<20μm) in the hamster cheek pouch by rendering cells fluorescent via a constant infusion of acridine orange. Electronic signals generated as cells passed a fixed observation site were obtained and analyzed as a stochastic point process. The stochastic features of cell transit were then evaluated in terms of the time between adjacent cells (TC) and number of cells per unit time (leukocyte flux). Data reported is based on sequential observation times of 600 s in each of five animals. No less than 400 leukocytes were observed in any experiment. Comparison of the observed frequencies of TC against expected values for Poisson, Gaussian and uniform distributions was done with chi-square & Kolmogorov-Smirnov tests for goodness of fit. Results of all experiments show that at a statistically significant level (p>.05), the distribution of TC can be characterized as Poisson. Results also indicate that under the same statistical guidelines, the leukocyte flux fits a Gaussian distribution.

48.8

QUANTITATIVE ANALYSIS OF THE CONTRACTILE CYCLE OF MESENTERIC TRANSPORTING LYMPHATICS.
J.N. Benoit, A.H. Goodman and H.J. Granger, Microcirculation Res. Inst. and Dept. of Med. Physiol. Texas A&M University, College Station, Texas 77843.

The contractile cycle of rat mesenteric transporting lymphatics was analyzed. Rats were anesthetized, the mesentery prepared for in vivo microscopic observation and a transporting lymphatic exhibiting spontaneous rhythmic contraction selected for study. Intralymphatic pressure(P) was monitored with a servo-null micropressure system and the rate of pressure development(dP/dt) determined for each contraction. Lymphatic diameter(D) and the rate of change of diameter(dD/dt) were also measured for each contraction. Stroke area change(ΔSA) and ejection fraction(EF) were calculated from the difference between end diastolic diameter(EDD) and end systolic diameter(ESD). Contractility indices for diameter(CID) and pressure(CIP) were calculated(CID=dD/dt/EDD; CIP=dP/dt/EDP). The time to peak pressure(TTPP) and interval between contractions(INT) were determined from the pressure tracing. Measurements were carried out in intermittent one minute intervals. A one minute sample of data from a single lymphatic is summarized as: Contraction Frequency 12/min; EDD-66.7±1.4μm; ESD-21.1±0.7μm; dD/dt-4.1±1.0μm/sec; ΔSA-3152.9±131.4$\mu m^2$; EF-0.90±0.005; EDP-3.17±0.04cm$H_2O$; ESP-4.22±0.06cm$H_2O$; dP/dt-1.99±0.13cm$H_2O$/sec; TTPP-0.58±0.05 sec; INT-5.01±0.26 sec; CIP-0.63±0.04/sec; CID-0.96±0.03/sec. The results of this study indicate that basic cardiac function indices can be used to analyze lymphatic function
(Supported by HL07247-01A1, RR05814, & HL21498 from NIH).

48.9

VASCULAR COMPLIANCE VS STARLING RESISTOR AS MECHANISM FOR ZERO FLOW PRESSURE IN DYNAMIC PRESSURE FLOW STUDIES.
S. Magder, McGill University, Mtl, PQ, Canada

Two hypothesis have been proposed to explain why arterial inflow (Qin) stops at a pressure (Pz = zero flow pressure) above venous pressure (Pout) in dynamic pressure-flow studies: (a) the presence of a Starling Resistor (SR) mechanism in the arterioles; (b) the vascular compliance. To separate these we studied isolated canine hindlimbs in which we controlled Qin or inflow pressure (Pin) with a pump and Pout with an external SR. We measured Qin and Pout with electromagnetic flow probes. Test 1. With SR, Qin and Pin should be independent of Pout until Pout=Pz. We therefore first measured Pz by decreasing Qin to 0 while measuring Qin and Pin, and then raised Pout in steps while either Pin or Qin were kept constant. Pz was 60-70 mmHg but Pout could only be raised to 14.4±8.9 or 17.2±5.9 mmHg (n=9) before affecting Pin or Qin respectively (change in Pout was 7.0±7.8 and 10.7±5.6 mmHg). Effects of venous pressure on Pz were excluded by showing that Qin = 0 when Pout = Pin. These findings suggest at most only a small SR exists. Test 2. If Pz is due to compliance, Pz should decrease as the time taken to get to Qin = 0 is increased whereas it should not change with a SR. We therefore varied time to Qin = 0 from 1 to 10 sec and found an exponential decrease in Pz with a rapid initial fall, but a Pz of 35-40 mmHg at 10 sec. The data fit a model with two compliances in series but not one compliance and were against the SR hypothesis.

## GRAVITATIONAL, ALTITUDE AND EXERCISE PHYSIOLOGY

49.1

A.M. KELLAS AND THE CHALLENGE OF MOUNT EVEREST.
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At the beginning of this century, many explorers cited three unattained goals: reaching the North and South poles, and ascending Mt. Everest. The first two were readily accomplished but the last took more than half a century. A.M. Kellas (1868-1921) was a British physiologist who made pioneering contributions to the exploration of Everest, and to the early physiology of extreme altitudes, but his contributions have been almost completely overlooked. Although he had a full-time faculty position at the Middlesex Hospital Medical School in London, he was able to make six expeditions to the Himalayas in the first two decades of the century and by 1919 when the first official expedition to climb Everest was being planned, he probably knew more about the approaches than anybody else. But his most interesting contributions were made in an unpublished manuscript "A Consideration of the Possibility of Ascending Mount Everest" where he discussed the problems of acclimatization, barometric pressure, alveolar $PO_2$ at extreme altitudes, and ascent rates near the summit. On the basis of an extensive analysis, he concluded that "Mt. Everest could be ascended by a man of excellent physical and mental constitution in first rate training without adventitious aids [supplementary oxygen] if the physical difficulties of the mountain are not too great". Kellas was one of the first physiologists to study extreme altitude and he deserves to be better known.

49.2

BLOOD PRESSURE (BP) AND FLOW (BF) TO THE HEAD IN A RHESUS MONKEY FLOWN ABOARD COSMOS 1514.
H. Sandler, V.P. Krotov*, J. Hines*, V.S. Magedov*, B. Benjamin, A.M. Badakeva*, B.M. Halpryn*, and V.S. Krilov*. NASA-Ames Research Center, Moffett Field, CA 94035 and Institute of Biomedical Problems, Moscow (USSR).

BP and BF to the head was measured in one (Bion, 5 years of age, 4.64 kg) of two chronically instrumented Rhesus monkeys flown aboard Cosmos 1514 (December 14-19, 1983). Values were measured from a cuff implanted about the left common carotid artery 53 days before flight. BP was sensed by a diaphragm strain gauge resistance transducer and BF using ultrasonic crystals. Data was collected 5 minutes every 2 hours around the clock. Information during flight was compared with identical data while on the launch pad (December 13-14) and from a 36-hour ground-based control period (December 4-6). Mean BP on insertion into orbit demonstrated an immediate 10% increase compared to control levels (96 mmHg) and 16-27% increase over the first few hours of flight before returning to baseline levels. Mean blood flow velocity showed an 8 cm/sec increase while on the launch pad which was maintained over the duration of the mission. Pressure-flow relationships to the head were shown to be altered with insertion into orbit. These changes persisted into the second day of flight and were most clearly indicated by a decrease in relative differences between blood flow to the head and total cardiac output measured by impedance plethysmography. Signs of adaptation appeared on Days 3-5 of flight.

49.3

THE EFFECTS OF SEATED AND HORIZONTAL HYPOKINESIA ON LOWER BODY NEGATIVE PRESSURE (LBNP) TOLERANCE IN RHESUS MONKEYS. Bruce M. Halpryn*, Delbert E. Philpott*, Harold Sandler. NASA/Ames Research Center, Moffett Field, CA. 94035

Body weight (BW) and plasma volume (PV) decreased as a result of 14 days of hypokinesia whether seated (S)(N=4) or horizontal (H) (N=3). H animals showed decreased tolerance to LBNP at 7 days that was even greater at 14 days (16±.3 vs 12±1.6 vs 7±1.5 mins)(ΔBW=.65±.67 Kg, ΔPV=-2.5±6.2 ml/Kg). A minimal change in response to LBNP was seen in S animals (19±1.0 vs 15±1.4 vs 17±1.5 mins) despite a greater loss of PV (ΔBW=.81±.21, ΔPV=-6.0±3.8 ml/Kg). Two caged control animals showed no significant change in tolerance to LBNP after removal of 10 ml/Kg of whole blood. Two H animals, at 14 days, had LBNP tolerance return close to pre-H levels after PV expansion with 8 ml/Kg Dextran 75 in saline. The myocardium of H showed significant degenerative ultrastructural changes at 14 days including increases in glycogen, lipid globules, and edema. These findings indicate that both a myocardial factor and PV play an important role in determining tolerance to LBNP.

49.4

ABSTRACT WITHDRAWN

49.5

EFFECTS OF HIGH ALTITUDE ON CARDIOVASCULAR, BODY FLUID, AND HORMONAL RESPONSES TO PASSIVE STANDING. J.R. Claybaugh, C.F.T. Uyehara*, C.E. Wade, J.L. Sondeen, W.S. Evans*, and W.S. Stokes*. Tripler Army Medical Center, Honolulu, HI 96859-5000, and Letterman Army Institute of Research, San Francisco, CA 94129-6800.

Six male subjects (ages 21-45) participated in two passive standing experiments, one at sea level (SL) and one at high altitude (HA, 4100 M) after at least 2 days of acclimation and no symptoms of acute mountain sickness. In each experiment, venous blood samples were obtained from the arm, without stasis, once after 30 min of quiet supine position and then after 15 min of passive standing while leaning with shoulders against a vertical support. Systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were also monitored. HA exposure was accompanied by increased HR and decreased plasma renin activity (PRA) and plasma protein concentration (Pprot) while in the supine position. Hematocrit (Hct) was increased ($P<0.063$, n=4, 2 lost samples) slightly, and there were no detectable changes in plasma osmolality (Posm), plasma antidiuretic hormone ($P_{ADH}$), SBP or DBP. After 15 min passive standing, Hct, Pprot, HR, DBP, PRA, and $P_{ADH}$ were increased at both SL and HA. The increase in Pprot was significantly greater at HA. Although the causes are not clear, the decrease in Pprot in the supine position at HA could be related to the associated fluid shifts at HA. Supported by U.S. Army Health Services Command and U.S. Army Medical Research & Development Command Grant #85PP5841.

49.6

EFFECTS OF THE COMPONENTS OF SOLAR RADIATION ON THE NEOPLASTIC POTENTIAL OF BALB C/3T3 CELL CULTURES. R. Pampin* H.S. Targovnik* and N.Z. Baturay* (SPON. J. Klavins). Pharmaceutical Sciences Dept., St. John's University, Jamaica, NY. 11439 and Dept. of Radiotherapy, Mt. Sinai Hospital, N.Y., N.Y. 10018.

Accumulated evidence suggests that the complex series of cellular interactions leading to cancer may be the result of an equally complex combination of environmental factors. Our findings indicate that UVA ($\lambda$ > 320 nm; near UV), long considered harmless, significantly promotes neoplastic cellular transformation in carcinogen initiated Balb C/3T3 mouse fibroblasts as well as acting as a cocarcinogen with UVB ($\lambda$ >290-320 nm, mid-UV). Only Type II and Type III foci were counted and these were found to grow in soft agar. UVA and UVB comprise the solar spectrum. Radiation was supplied by an Oriel Solar Simulator with appropriate filters.

Sister chromatid exchange (SCE), induction, an indication of cytogenetic changes often correlated with mutation, increases linearly as a function of UVA and UVB dose.

On the molecular level, UVA appears to affect normal DNA repair kinetics. Pyrimidine dimers, one of the major forms of DNA damage caused by germicidal UV ($\lambda$ <290 nm; far UV), are repaired by an excision process which is measured by the loss of enzyme sensitive sites. Although UVA alone does not appear to affect pyrimidine dimer inductions when cells are pretreated with increasing doses of near UV, followed by a single dose of UV at 254 nm, there is a dose dependent inhibition of the removal of enzyme sensitive sites.

49.7

A DYNAMIC SYSTEM FOR EXPERIMENTAL HUMAN EXPOSURE TO OZONE. S.M. Fadl*, D.R. Stirling*, D.W. McKenzie* (Spon. G. Quamme). School of Kinesiology, Simon Fraser University, Burnaby, B.C., V5A 1S6

The production and management of ozone concentrations that are equitable for experimental human exposure can technically present many problems. A dynamic system was designed and tested for reliable production of 0.35 ppm ozone in an environmentally controlled chamber using a "Authacon" 1200 ozonier and ambient air sources in place of pure oxygen. Dilutent air flows of 80-120 litres/minute were selected to simulate an anticipated range of minute volumes of Ventilation ($\dot{V}_E$) of human subjects at desired experimental conditions. Over the range of air flows corresponding concentrations of ozone (X = 0.30 ± 0.02 ppm, range = 0.26 ± 0.52 ppm) were observed. Two standard techniques were used simultaneously for the determination of the ozone concentration over a one hour period. A precalibrated direct reading ozone monitor (Mast co. model 714-4) was used to record continuously the concentration of ozone in air (ppm) along with a second independent midget impinger system. The impingers were analyzed using the NIOSH spectrophotometric technique. Using multiple regression analysis techniques no differences were observed for the measured concentrations of ozone using the two sampling procedures. The dynamic system developed during this study was an efficient method of ozone generation and when compared to other systems previously reported in the literature, the ozone produced was under safer conditions, less expensive and maintained a high degree of reliability under conditions of multiple and variable levels of air flow.

49.8

VALIDITY OF $\dot{V}O_2$max CRITERIA FOR ARM CRANK TESTS. G.M. Davis,* F.J. Servedio,*2 A.G. Suryaprasad,* S.C. Gupta,* V. Stull* and R.M. Glaser. Wright State University School of Medicine, Miami Valley Hospital, V.A. Medical Center, Dayton, OH 45435.

Forty-eight male paraplegics ($\bar{x}$ age=27.9 ± 1.0 yr) performed multiple assessments of arm crank $\dot{V}O_2$peak for the purposes of: 1) examining whether or not subjects (S) satisfied traditional leg $\dot{V}O_2$max criteria; and, 2) exploring alternative strategies for defining the $\dot{V}O_2$max plateau. Throughout 70 maximal arm tests, 90% of S satisfied the criteria that RPE ≥ 7 (10-point Perceived Exertion scale), 83% demonstrated RERmax ≥ 1.1, and 63% showed a $\Delta\dot{V}O_2$ < 2.1 ml/kg/min between the final 2 workloads (Taylor criterion). Only 50% of S satisfied accepted criteria that HRmax ≥ ±15 bpm of age-predicted maximal HR, and less than 25% demonstrated a $\Delta\dot{V}O_2$ < 54 ml/min between the final 2 workloads (Mitchell criterion). Analysis of S above and below the mean $\dot{V}O_2$peak (26.7 ± 1.3 ml/kg/min) suggested that the efficacy of traditional criteria were affected by body size and fitness level. Three new criteria based on individual or group responses to a specific maximal test protocol (Freedson et. al., 1986) increased the proportion of S meeting $\dot{V}O_2$max criteria to 40-66% in all subjects and were less sensitive to differences of body dimension and $\dot{V}O_2$peak. These data suggest that criteria used to establish a $\dot{V}O_2$max plateau during arm exercise should take into account possible peripheral limitations to effort.

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49.9

EFFECTS OF TRAINING ON THE METABOLIC AND RESPIRATORY PROFILE OF HIGH-INTENSITY EXERCISE. D.C. Poole, S.A. Ward & B.J. Whipp, UCLA, Los Angeles & Harbor/UCLA Med Ctr, Torrance, CA

For exhausting cycling, power (P) may be well described as a hyperbolic function of work duration (t): $P=(W'/t) + \theta f$, where $\theta f$ is a "fatiguing threshold" (occuring above the anaerobic threshold, $\theta_{an}$) and W' represents a constant (kJ). As $\theta f$ is increased by training (and W' is unaffected), we chose to explore the metabolic and gas-exchange basis for this effect. Prior to and immediately following interval training, healthy males completed: an incremental cycling test (25 W/min) to determine $\theta_{an}$ and $\dot{V}O_{2max}$; 5 exhausting constant-load tests to determine $\theta f$ and W'; a constant-load test at $\theta f$ (24 min) and at $\theta f$ + 15W to fatigue to determine temporal profiles of gas exchange, blood-gas, acid-base and metabolic response. Gas exchange variables were monitored each breath; arterialized venous blood (dorsum of heated hand) was sampled regularly. Training increased $\dot{V}O_{2max}$ by 13%, $\theta f$ by 10% and $\theta_{an}$ by 39%. At each stage of training $\dot{V}O_2$, blood lactate and pH all eventually stabilized for the "$\theta f$" test. However, during the "$>\theta f$" test, $\dot{V}O_2$ and lactate continued to rise and pH fell until fatigue ensued. Norepinephrine and epinephrine levels, body temperature and $\dot{V}_E$ rose progressively throughout both tests. The "fatigue threshold" for exhausting work thus appears to represent the upper limit for stability of $\dot{V}O_2$, blood lactate and pH. We conclude that exercise above $\theta f$ is characterized by a steadily increasing $\dot{V}O_2$ and blood lactate, a falling pH and consequently, imminent fatigue.

49.10

EFFECTS OF SMOKING ON PHYSICAL PERFORMANCE IN MILITARY PERSONNEL. William L. Daniels, Patricia Fitzgerald,* Joseph Dziados,* Robert Mello* and James A. Vogel. U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760.

Six hundred eighty-five male military personnel between the ages of 18 and 39 years were evaluated to determine the effects of smoking on laboratory and field measures of physical performance. Subjects were divided into three groups based on smoking history; non-smokers (NS), smokers (S) and ex-smokers (ES). Measures of physical performance decreased with age in all groups, but the decline was greater in smokers than in non-smokers. Results also showed greater caloric expenditure in recreational activity for non-smokers versus smokers. An analysis of covariance with age and caloric output in recreational activity as covariates gave the following results:

| | NS | S | ES | F-Ratio | P-Value |
|---|---|---|---|---|---|
| 2-mile run (min) | 14.44 | 15.34 | 15.13 | 3.06 | 0.001 |
| Sit-ups (reps) | 56.62 | 52.87 | 52.63 | 8.92 | 0.05 |
| Push-ups (reps) | 55.30 | 50.86 | 51.43 | 2.25 | 0.005 |
| $VO_2$max (ml/kg/min) | 49.73 | 47.20 | 46.52 | 6.94 | 0.001 |
| Dynamic Lift (lbs) | 132.85 | 126.58 | 128.41 | 2.39 | NS |
| HRmax (bts/min) | 192.88 | 190.31 | 192.05 | 6.15 | 0.005 |

Results indicate that smoking has deleterious effects on physical performance that are independent of age and physical activity history.

49.11

INSULIN AND SUBSTRATE UTILIZATION IN RESPONSE TO PROLONGED EXHAUSTIVE EXERCISE IN WOMEN. J.L. Durstine, M.L. Rocchio, P.E. Smith, M.D. Senn and W.P. Bartoli (SPON: S.K. Powers) Dept. of Phys. Ed., Univ. of S. Carolina, Columbia, SC 29208

The effect of prolonged exhaustive exercise on insulin response and substrate utilization has been studied in men, but little attention has been given to these changes in women. The purpose of this study was to observe changes in insulin, glucose, lactate, glycerol and free fatty acid (FFA) in women during and after prolonged exhaustive exercise. Ten women (mean age 20 yrs) walked to exhaustion on a treadmill at a speed and grade requiring 45% of their $\dot{V}O_{2max}$. Venous blood (5 ml) was obtained 24 hr and immediately prior to exercise, immediately before exhaustion (5.1 hr), 30 min and 24 hr following exhaustion. Water (150 ml) was provided every 30 min to prevent dehydration. Pre-exercise values were: glucose 95 ± 4 mg/dl; FFA 0.62 ± 0.10 mmol/L; lactate 0.70 ± 0.13 mmol/L; glycerol 0.10 ± 0.01 mmol/L; insulin 3.73 ± 0.43 mmol/L (values are means ± $S_e$). At exhaustion, significant increases were found in FFA (1.48 ± 0.15), lactate (1.90 ± 0.27) and glycerol (0.67 ± 0.08). These variables were still elevated after 30 min of recovery, but were normal at 24 hr post-exercise. Insulin was lower after 30 min of exercise (2.44 ± 0.25) and remained lower during the exercise period. Within 30 min of recovery insulin returned to rested values. These data indicate that insulin, FFA, lactate and glycerol are affected by acute exhaustive exercise in women while glucose is not.



53.1

DO CALCIUM INHIBITORS PREVENT FREE RADICALS' RELEASE DURING PROLONGED HYPOTHERMIC RENAL ISCHEMIA? D. Anaise*, L. Ramsammy*, B. Lane* and F.T. Rapaport* (SPON: Lorne Mendell ). SUNY at Stony Brook, Stony Brook, N.Y. 11794-8192

Free radicals release is increasingly recognized as a prime mediator of cellular injury during renal ischemia. We have previously shown that the calmodulin inhibitor, trifluoperazine (TFP) protected the microcirculation and subsequent function of kidneys flushed with Collins' solution (C) and preserved in the cold for 72 hours. It was suggested that TFP may exert its protective effect by blocking the coversion of xanthine dehydrogenase (XD) to xanthine oxidase (XO) - a key reaction in the liberation of free radicals. In order to assess this important question, 10 mongrel dogs underwent bilateral nephrectomy. The right kidney was flushed with C and the left with C+TFP. Both were stored in the cold for 48 and 72 hours and were then transplanted to the femoral vessels of another dog. Renal blood flow (RBF) was monitored for one hour. A sharp decrease in RBF from 2.2 to .29 cc/gm/min was noted in C flushed kidneys. In contrast, RBF of 1.27 cc/gm/min was maintainedin C+TFP flushed kidneys ($P<0.001$). Cortical biopsies for Malondialdehyde (MDA) and XO-XD ratio were assayed before and after perfusion. Lipid peroxidation (MDA release) was more pronounced in C+TFP flushed kidneys (1.45 ng/mg/prot) than in C flushed kidneys (.78). XO-XD ratio was similar in both groups. No increase in MAD or XO-XD ratio was noted after reperfusion in both groups. Taken together the data suggests that protective effects of TFP can not be attributed to protection from free radicals' release.

53.2

RENAL RESPONSE TO HEMOGLOBIN SOLUTIONS. Arthur L. Rosen, Lakshman R. Sehgal*, Steven A. Gould*, Hansa L. Sehgal*, Richard DeWoskin* and Gerald S. Moss*. Dept. of Surgery, Michael Reese Hospital & Medical Center Chicago, Illinois 60616.

Clinical trials with tetrameric stroma-free hemoglobin solutions (T-SFH) demonstrated that T-SFH produced transient bradycardia, hypertension, and declines in endogenous creatinine clearance (GFR) and urine volume. Animal studies did not reliably predict these effects of T-SFH. We report on the transient response to T-SFH by a nonhuman primate. Thirteen unanesthetized well hydrated baboons were infused either with Ringer's Lactate (N=6) or T-SFH (7 gm/dl) at a rate of 15 cc/kg over a one hour period. Values (mean ± S.E.M.) during this period for the animals receiving T-SFH are shown:

| | Baseline | Post-Infusion (T-SFH) |
|---|---|---|
| Heart Rate(bpm) | 114 ± 9 | 90 ± 7* |
| MAP (torr) | 114 ± 4 | 133 ± 3* |
| Urine Output(cc) | 201 ± 48 | 91 ± 22* |
| GFR (cc/min/m$^2$) | 87.9 ± 7.5 | 67.2 ± 5.8* |

*Change significant ($p < .025$). There were no significant changes in the baboons receiving RL. Conclusion: This animal model reproduces the hemodynamic and renal effects of T-SFH seen in humans. (Supported by Northfield Laboratories, Northfield, IL.)

53.3

THE ACUTE EFFECTS OF RADIOCONTRAST ON RENAL FUNCTION IN CONSCIOUS DIABETIC RATS. Rebecca Papendick*, Helen Alpert* and Carlos A. Vaamonde. VAMC and Department of Medicine, University of Miami, Miami, Florida 33125.

The mechanism(s) whereby diabetic (DM) patients develop acute renal failure after iv radiocontrast injection (RC-ARF) remains unknown. In anesthetized DM rats, RC causes a decrease in GFR and renal blood flow, suggesting that hypoxic injury may underlie RC-ARF. The renal effects of 5 ml/kg bw iv Renografin 76% (sodium meglumine diatrizoate) were studied in 7 diabetic (streptozotocin, 60 mg/kg, given 3 months before) and 7 control (C) conscious, female, Sprague-Dawley rats. GFR (ml/min/g kidney wt) was measured by $^{14}$C-inulin for 3 h. Data are in X±SE.

| | Baseline | | | Peak | GFR after RC | |
|---|---|---|---|---|---|---|
| | GFR | MPB | FENa | FENa | 40' | 120' |
| C | 1.6±.1 | 130±2 | 0.2±.1 | 5.5±1 | 1.5±.1 | 1.4±.2 |
| | NS | < .01 | < .01 | NS | NS | NS |
| DM | 1.5±.1 | 122±2 | 0.8±.2 | 6.1±1 | 1.4±.1 | 1.3±.1 |

MPB = mean blood pressure (mm Hg); FENa=Fract. Na excretion (%).

Baseline GFR and Hct were not different, but urine flow, Cosm and FENa were higher and MBP lower in DM rats. After RC-injection, MBP remained lower in DM. The magnitude of the RC-induced diuresis was similar in both groups. GFR was not changed by RC and remained similar between groups. In conclusion, in unanesthetized non-dehydrated DM rats, the acute administration of radiocontrast material does not decrease GFR despite a sustained reduction in mean blood pressure.

53.4

EFFECT OF DIETARY Na ON THE IN VITRO RENIN SECRETORY EFFECTS OF N$^6$-CYCLOHEXYLADENOSINE (CHA) IN RATS

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Previous observations by others have shown that Na deprivation and Na loading augment and attenuate, respectively, the inhibitory effect of adenosine on renin secretion in vivo. The purpose of the present experiments was to test the hypothesis that Na deprivation and Na loading alter the sensitivity of the adenosine receptors ($A_1$ subclass) which mediate the inhibitory effect. The rat renal cortical slice preparation was used. CHA, an adenosine analog which selectively activates the $A_1$ subclass of receptors in the nM-μM range, inhibited renin secretion over the same range of concentrations (nM-μM) and to about the same maximal extent (to 50% of the mean basal secretory rate) in cortical slices taken from Na loaded, control, and Na deprived rats. At concentrations above 1 μM CHA can activate $A_2$ as well as $A_1$ receptors, and over the range 1-50 μM, CHA produced a relative stimulation of renin secretion, mediated by $A_2$ adenosine receptors, which also was independent of the previous dietary Na intake of the rats. These results demonstrate that changes in the intrinsic sensitivity of adenosine receptors do not explain dietary Na-induced changes in the in vivo renin secretory response to exogenous adenosine. Some other mechanism (e.g., changes in the concentration of endogenously-released adenosine) must be invoked to explain this phenomenon.

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53.5

EFFECTS OF XANTHINE AMINE CONGENER (XAC) AND THEOPHYLLINE (TH) ON N$^6$-CYCLOHEXYLADENOSINE (CHA) INDUCED RENAL VASOCONSTRICTION

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Wayne State University, Detroit, MI and NIH, Bethesda, MD.

Adenosine (AD) and AD analogs selective for the $A_1$ subclass of AD receptors such as CHA produce renal vasoconstriction in vivo and in vitro. To examine the effects of the AD receptor antagonists XAC and TH, studies were performed in isolated rat kidneys perfused at constant flow with a non-recirculated medium (Krebs-Henseleit saline supplemented with 3.5 g% Ficoll, 1 g % albumin, 180 mg % glucose and 89 mg% b-alanine). After a 45 min period of equilibration at a pressure of 100mm Hg, flow was maintained at the rate obtained during the final 15 min of equilibration and pressure was allowed to vary. Changes in pressure (ΔP) were measured as the difference in pressure from baseline in response to CHA, in the presence or absence of antagonist. $10^{-8}$ and $3x10^{-8}$ M CHA resulted in ΔP's of 5 + 2 and 21 + 5 mm Hg respectively. TH at $5x10^{-5}$ M produced a shift in the dose-response relationship such that three times the concentration of CHA was required to produce the same response; XAC at 2 x $10^{-8}$ M produced a similar shift. The calculated inhibitory constants, $K_i$, for TH and XAC were $2.6x10^{-5}$ and $1x10^{-8}$, respectively. Thus, XAC is three orders of magnitude more potent than TH in blocking CHA-induced renal vasoconstriction.

Supported by the National Institutes of Health (HL 24880).

53.6

EFFECT OF DIPYRIDAMOLE (D) ON THE INITIATION PHASE OF ISCHEMIC ACUTE RENAL FAILURE (ARF). J. J. Lin*, P. C. Churchill and A. Bidani. Dept. Physiol., Wayne State Univ., Detroit, MI 48201

To test the hypothesis that increased extracellular adenosine(Ado) during ARF mediates the hemodynamic changes, 3 groups (gr) of nembutal-anesthetized rats subjected to 30 min of left renal artery clamping were studied. 30 min after reflow, a 40-min clearance was begun during which blood pressure (BP, mmHg), inulin clearance ($C_{in}$, ml/min/Kg), plasma flow (PF, ml/min/Kg; left, PAH clearance/PAH extraction; right, PAH clearance), urine flow (V, ul/min/Kg) and fractional Na excretion ($FE_{Na}$, %) were measured. Gr C(n=11) received a 0.055 ml/min saline vehicle. Gr D(n=12) and gr D+T(n=11) respectively received D alone (24 ug/min/Kg) or D plus theophylline (111 umol/Kg bolus, 1.1 umol/Kg /min infusion) 15 min before the occlusion and then throughout the experiment. Data are means±SEM; p 0.05, *D vs C, #D+T vs D.

| gr | kidney | BP | $C_{in}$ | PF | V | $FE_{Na}$ |
|---|---|---|---|---|---|---|
| C | Lt | 117±2 | 2.4±0.1 | 9.2±0.5 | 214±23 | 11.0±1.2 |
| | Rt | | 4.5±0.2 | 10.6±0.8 | 29±4 | 0.8±0.4 |
| D | Lt | 112±3 | 1.6±0.1* | 8.7±0.6 | 153±19* | 12.5±1.7 |
| | Rt | | 4.4±0.2 | 10.9±0.7 | 31±4 | 0.8±0.2 |
| D+T | Lt | 100±4# | 2.5±0.1# | 13.0±1.5# | 350±32# | 17.1±1.2# |
| | Rt | | 3.6±0.6# | 9.3±1.0 | 16±1# | 0.3±0.1# |

As shown above, D (Ado uptake blocker) pretreatment (pretx) decreased $C_{in}$ and V of Lt kidneys. Since theophylline (Ado antagonist) pretx, under the presence of D, had opposite effects as D pretx did, our study supports this hypothesis.

53.7

ANGIOTENSIN II-MEDIATED RENAL VASOCONSTRICTION DURING CALCIUM CHANNEL BLOCKADE. L. Gabriel Navar and Phillip R. Gibson*. University of Alabama at Birmingham, Birmingham, Alabama 35294

Previous studies have suggested that angiotensin II (AngII)-induced renal vasoconstriction is mediated by two cellular mechanisms which may be segmentally distinct. One component is sensitive to calcium channel blockers while the other component can still be manifested in the presence of calcium channel blockers. The present experiments were conducted to quantify the calcium channel dependent and independent effects of AngII on renal blood flow and GFR. Anesthetized dogs (N=8) were pretreated with an AngII converting enzyme inhibitor (MK422; .2 mg/kg) to reduce endogenous AngII levels. Angiotensin II was infused into the renal artery at doses (.03μg/min·kg) sufficient to elicit an average decrease in RBF by 21±4 %; GFR decreased by 16±4 %. After recovery, verapamil was infused into the renal artery (5μg/min·kg). New control values were obtained and AngII was infused at the same doses previously used. Although the vasoconstriction response was blunted, RBF was still reduced by 13 ± 2%. During verapamil exposure, AngII did not significantly alter GFR, and no antinatriuresis was observed. These results provide further evidence that the angiotensin sensitive component of the renal vasculature that is sensitive to calcium channel blockade is responsible for the ability of AngII to reduce GFR.

53.8

**VERAPAMIL INFUSION BLOCKS THE POSTPRANDIAL INCREASE IN RENAL BLOOD FLOW** Robert G. Carroll, Cindy M. Wilson,* and Marvin E. Whitehurst.* Department of Physiology, East Carolina University School of Medicine, Greenville, NC 27834

Ingestion of a protein rich meal causes a 20%-30% increase in renal blood flow which is maintained over three hours. The mechanism underlying this response, however, is currently unknown. These experiments examined the postprandial renal hyperemic response during infusion of the calcium antagonist verapamil. The renal arteries of six male dogs were fitted with electromagnetic flow probes and the femoral vessels catheterized. Ten days after surgery, the dogs were fed 10g lean beef/Kg body weight, and infused alternatively with saline or verapamil (.9 mg bolus, .06 mg/min sustaining). The % increase in renal blood flow (RBF) is shown below.

| Time (min) | 0 | 30 | 60 | 120 | 180 |
|---|---|---|---|---|---|
| RBF (saline) | control | 20 = 8 | 22 = 4 | 25 = 4 | 22 = 5 |
| RBF (verapamil) | control | 15 =10 | 10 = 6 | 4 = 5 | 10 = 2 |

Verapamil eliminated the postprandial renal hyperemic response. Two possible theories may account for these results. Verapamil may prevent the release of a vasodilator agent. Alternatively, verapamil may prevent the renal afferent arteriole from responding to the normal vasodilatory stimulation. Further experiments are necessary to decide between these two theories. Supported in part by North Carolina Affiliate, AHA.

54.1

MONOPHASIC ACTION POTENTIALS RECIRDING FROM HUMAN OR ANIMAL HEART IN SITU BY USING A CONTACT ELECTRODE. JT Xie*. ZC Li*. YS Shi*. Biology Dept. Nankai University. Tainjin. PR China. 300072

Monophasic action potential (MAP) can be recorded from endocardial or epicardial surface of the heart, encluding man (n=10), dog (n=10), rabbit ( n=25) and toad (n=15), by using a conventional cardiac catheter or an epicardial electrode without suction electrode. The study showed that 1) there were different parameters of MAP in the different subject or animal heart, for example, MAP amplitude of canine left ventricular epicardium (33±7.8 mV) was higher than rabbit (23±4.9 mV); 2) there were different parameters of MAP in the different site of the same heart, for instance, MAP amplitude of human or canine ventricle was higher than atria; 3) some drugs might change MAP duration, such as verapamil and procainamide etc. Verapamil (10 mg) markedly increased in the slope of phase 2 and 3 and shortened $MAPD_{50}$ in human right ventricular endocardium. We conclude thet the method of recording MAP by using contact electrode can be applied both in the clinic and experimental cardiac electrophysiologic study.

54.2

SELECTIVE EFFECTS OF ACETYLCHOLINE AND SUCCINYLCHOLINE ON POTASSIUM CHANNELS IN HEART CELLS. J.K. Bubien* and W.T. Woods, Jr., Univ. of Alabama at Birmingham 35294.

Electrophysiological mechanisms that mediate muscarinic receptor effects in atria and ventricles differ. This was examined in single $K^+$ channels of canine atrial and ventricular sarcolemma verified by reversal and $K^+$eq. Channels were observed in cell-attached patches only when pipette $[K^+]$ = 70 mmolar or more. However, 2 types of channels were observed in inside-out patches when pipette $[K^+]$s = 5 mmolar. Acetylcholine (ACh, $10^{-7}$M) increased chord conductance (g) (+100%) and probability of being open (300%) of kinetically slow ($\tau$ open > 50 msec; $\tau$ closed > 50 msec) $K^+$ channels for inside-out patches of atrial sarcolemma. Kinetically faster $K^+$ channels ($\tau$ open = 2.4 msec; $\tau$ closed1 = 0.8 msec; $\tau$ closed2 = 50 msec) were unaffected by ACh up to $10^{-3}$M. Succinylcholine (SCh) produced the same qualitative effects as ACh on the kinetically slower channel but at 100x the [ACh]. SCh ($2x10^{-3}$M) shifted reversal potential from -10 mv to -50 mv and reduced percent open time from 30% to 10% in $K^+$ channels from ventricular myocytes (cell-attached). SCh changed opening pattern from long events to bursts of brief events with periods of quiescence. G of this channel was blocked; g of the atrial channel was enhanced by SCh. Characteristics of $K^+$ channels depended upon type of patch, pipette $[K^+]$, and ACh or SCh. SCh enhanced $gK^+$ in atrial and reduced $gK^+$ in ventricular cells.

54.3

HYPOXIA AND REOXYGENATION INDUCED CHANGES IN SLOW RESPONSE ACTION POTENTIAL.
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Slow response action potentials(SRAP) were studied in canine ventricular muscle tissue during hypoxia (Nitrogenated solution, 95%$N_2$; 5%$CO_2$) and reoxygenation (97%$O_2$; 3%$CO_2$). Slow responses were initiated by perfusing the tissue with a solution containing 27mM KCl and $10^{-6}$M norepinephrine(other ions as in Tyrode, except NaCl adjusted to maintain osmolarity). The tissue was stimulated at 0.5Hz,20V, and 4ms(duration). Microelectrode technique was used to record action potentials and mechanical activity was recorded with a force displacement transducer. The SRAPs could be abolished by $MnCl_2$ (1-2mM) while tetrodotoxin ($5x10^{-6}$M) had no appreciable effect. During hypoxia the amplitude of the SRAP reduced steadily with time, action potential duration(APD) at all levels were shortened and rate of rise was less than that in oxygenated solution. After hypoxia(20-30min), reoxygenation produced a larger amplitude action potential than in prehypoxic stage and APD was shorter. These changes in amplitude and duration were similar to that when $(Ca)_o$ was increased from 2.7mM to 8.1mM in oxygenated solution. We conclude that reoxygenation increases calcium influx in muscle tissue.

54.4

INFLUENCE OF SLEEP STAGE ON VENTRICULAR REFRACTORINESS.
Gaetane C. Francis*, Eric L. Hagestad*, Richard L. Verrier, Cardiovascular Laboratories, Harvard School of Public Health, Boston MA 02115.

Sleep is associated with substantial changes in autonomic nervous system activity. It is unknown, however, whether these are reflected in alterations in the heart's electrophysiological properties. The effects of rapid eye movement (REM) sleep and slow wave sleep (SWS) on ventricular refractoriness were studied in chronically instrumented cats. Electrodes were implanted to record electro-oculograms, electromyograms, and electroencephalograms for sleep stage determination. A right ventricular catheter was employed for cardiac electrical testing using the single stimulus technique. All determinations were made during fixed rate pacing. The following results were obtained (mean ±SEM *p<0.05 vs awake):

| | Heart Rate (beats/min) | Effective Refractory Period (msec) |
|---|---|---|
| Awake | 170±10 | 114±4 |
| REM | 140±7* | 124±3* |
| SWS | 140±3* | 121±2* |

These results indicate that both REM and SWS prolong the refractory period compared to the awake state. The changes in refractoriness during sleep are comparable to those observed during vagal activation or withdrawal of sympathetic neural activity. Further investigation will be required to determine the precise neural mechanisms involved.

54.5

EFFECT OF (-) BAY K 8644 ON CA CURRENTS IN CULTURED NEONATAL RAT VENTRICULAR MYOCYTES. A.E. Lacerda* and A.M. Brown. Dept. Physiology & Molec. Biophys., Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030.

Primary cultures of neonatal rat heart ventricular myocytes produce small isolated spherical cells ideal for voltage clamp procedures using the whole-cell patch clamp method. Records of Ca channel tail currents in 5 mM Ca show two components of decay when the cell is held at -50 mV, stepped to 20 mV and returned to potentials from -90 to -40 mV. Both fast and slow components are voltage dependent and differ by a factor of approximately four at -50 mV. The (-) stereoisomer of the dihydropyridine Ca channel agonist Bay K 8644 (methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate) specifically increases divalent ion currents through high threshold Ca channels. In the presence of Bay K 8644 both fast and slow time constants of Ca tail current decay increase. This increase shows a concentration-dependent effect with an approximate $ED_{50}$ of 5 X $10^{-7}$ M for the slow component. Single channel data are consistent with the occurrence of a concentration-response relation for the increase of channel open time produced by Bay K 8644. A mode-changing model in which Bay K 8644 changes the relative probabilities among modes (Hess et. al., Nature 311: 538, 1984) cannot explain these results. The results are consistent with models in which some transitions within a given mode are modified by the drug. Supported by HL25145 and HL07348.

55.1

FUNCTIONAL PRESERVATION OF MYOCARDIUM AFTER THREE HOURS OF CARDIOPLEGIA IN RAT AND DOG. R.L. Kao, L.P. Arelt*, C. Mantini*, D. Wolfenberger*, P. Ku* and G.J. Magovern*. Allegheny-Singer Research Institute, Pittsburgh, PA 15212.

The goal of this study is to test the hypothesis that myocardial damage during reperfusion can be minimized or prevented if normal metabolic parameters can be maintained or restored before reperfusion. Isolated perfused working rat hearts subjected to elective cardiac arrest at 16° C were used to devise the best arresting solution and modality of administration. Both metabolic parameters (myocardial adenine nucleotides, creatine phosphate, lactate and glycogen levels) and hemodynamic performances (systolic and diastolic pressures, heart rate, cardiac output, contractility) before and after cardioplegia were used to assess the best arresting conditions. The best cardioplegic solution was further evaluated by using dogs under cardiopulmonary bypass. Right femoral artery and vein were catherized for blood pressures and samples. Cardiopulmonary bypass was achieved by using roller pumps with cannulation of the right atrium and left femoral artery. Cardiac output and contractility were estimated after installation of a Swan-Ganz catheter through the right jugular vein. Myocardial temperature was maintained between 12-18°C during crossclamp with 3 L cardioplegic solution used for each dog. Before and after 3 hr cardioplegia the cardiac output (2.64±0.21 vs 2.76±0.24 L/min), systolic pressure (103±7 vs 111±14 mmHg), and diastolic pressure (64±9 vs 62±4 mmHg) were well preserved. Myocardial ATP was 27.7 μ mol/g dry heart during reperfusion. With the best cardioplegic condition, all of the measured myocardial functions were preserved after three hours of elective cardiac arrest.

55.2

EFFECTS OF PYRUVATE ON GLUCOSE AND LACTATE UTILIZATION IN ISCHEMIC AND POST-ISCHEMIC ISOLATED WORKING HEARTS. R.T. Mallet, D.A. Hartman*, and R. Bünger. Dept. of Physiology, Uniformed Services University, Bethesda, MD. 20814-4799.

We have previously shown (Fed. Proc. 45:1040, 1986) that isolated working guinea pig hearts perfused with oxygenated (95 $O_2$/5 $CO_2$) Krebs-Henseleit buffer (pH 7.4; 2.5 mEq/L $Ca^{++}$) supplemented with 5 mM glucose and 5 mM lactate exhibited improved hemodynamic recovery in the presence of 2 mM pyruvate following 45 minutes low-flow mild acidotic ischemia. In the present study, rates of exogenous substrate utilization during preischemia, late ischemia, and postischemic reperfusion were enzymatically measured. Coronary flow during preischemia (~ 8 ml/min x g w wt) and late ischemia (~ 1.7 ml/min x g) was not affected by pyruvate supplementation. Ischemia did not appreciably alter glucose utilization but produced net lactate release instead of uptake. Pyruvate stimulated glucose utilization minimally in ischemia (1.6 vs. 1.5μmole/min x g; p<0.01). During reperfusion, pyruvate supplementation produced a greater increase in coronary flow and allowed lactate uptake instead of release. Under these conditions exogenous substrate balance, expressed as C3 units, was stimulated severalfold by pyruvate. In summary, glycolytic flux is not appreciably stimulated by pyruvate during mild acidotic ischemia. However, lactate utilization by the injured reperfused heart is influenced by the cytosolic redox state. Pyruvate stimulation of C3 utilization suggests pyruvate-dependent improvement of oxidative metabolism during postischemia.

55.3

MYOCARDIAL TOLERANCE TO GLOBAL ISCHEMIA: IMPORTANCE OF AGE AND SPECIES OF ANIMAL. *C. Wittnich,* C Peniston,* R.C.-J. Chiu,* T.A. Salerno.(SPON: A. Slutsky) University of Toronto, Toronto, Canada M5B 1W8.

Conflicting reports exist as to whether neonatal hearts are more or less tolerant to global ischemia than adults; one explanation is that species differences exist. The purpose of this work was to clarify this conflict by measuring the time interval between the onset of ischemia and the beginning of contracture (TIC), which correlates with the depletion of high energy phosphates, and is a useful index of sensitivity to ischemia. We compared the TIC in neonatal and adult dog and pig hearts. Puppies (3-5 days old) and adult dogs were anesthetized with Nembutal (30mg/kg). The hearts were rapidly excised and placed in a substrate-free Krebs-Henseleit bath. Myocardial temperature was kept constant at 37° C, and a left ventricular (LV) balloon was inserted and inflated to 10 mmHg. TIC was recorded by increase in the isometric LV balloon pressure. Results are expressed as Mean ± SEM and compared using Students t-test. This study was then repeated in pigs.

| | N | TIC(min) | P value |
|---|---|---|---|
| puppy | 4 | 37.0±2.7 | |
| adult | 4 | 59.0±5.6 | 0.0125 |
| piglet | 6 | 29.5±1.7 | |
| adult | 6 | 43.0±2.9 | 0.001 |

Thus it can be seen that in both dogs and pigs neonates show significantly decreased TIC compared to adults. Dogs showed significantly longer TIC than pigs (p<.05). It is concluded that the normal neonatal myocardium is indeed more vulnerable to global ischemia; this is not species specific. This has clinical implications in optimizing myocardial preservation, both for pediatric cardiac surgery and transplantation.

Supported by a grant from Deans Fund, U. of Toronto.

55.4

ADENOSINE RELEASE AND HIGH ENERGY PHOSPHATE LEVELS OF ISOLATED GUINEA PIG HEARTS. M.X. He*, R.D. Wangler, G.D. Romig* and H.V. Sparks. Michigan State U., East Lansing, MI. 48924

We tested the hypothesis that adenosine (ADO) released from isolated guinea pig hearts (n=5) in response to norepinephrine (NE) is regulated by the cellular phosphorylation potential (PP). $^{31}$P-NMR was used to measure the relative concentrations of inorganic phosphate (Pi), creatine phosphate (CrP) and adenosine triphosphate (ATP). Hearts were perfused with a physiological salt solution using 0.1 mM Pi. Venous effluent was collected for measurement of ADO and $PO_2$. After a control period, NE ($6x10^{-8}$M) was infused for 20 min. $^{31}$P-NMR spectra were collected every min. as were samples of venous effluent. During NE, PCr decreased rapidly to 72% of control (p<.01) after 8 min., and then recovered to 80% of control for the remaining 12 min. ATP fell slowly to 70% of control (p<.01) over 20 min. Pi increased to a peak at 2 min., then declined slowly to a steady state (60% of the peak and 3.5 X control) from 8 to 20 min. ADO release reached a peak (250 pmol/min/g, P<0.01) at 7 min. and then slowly fell to a steady state of 110 pmol/min/g from 10 to 20 min. PP (log[ATP]/[ADP][Pi]) fell rapidly to 63% of control (p<.01) at 5 min., remained there until 7 min., then slowly rose to 73% of control by 17 min. and remained at this level. There is a hyperbolic relationship between ADO release and PP, as PP reaches a certain limit, ADO release rapidly rises. These data support the hypothesis that ADO release is regulated by the cellular PP as a closely related variable. USPHS HL 24232.

55.5

ELECTRON PARAMAGNETIC RESONANCE EVIDENCE OF FREE RADICAL PRODUCTION DURING NO FLOW MYOCARDIAL ISCHEMIA. P.S. Rao* M.A. Crowder*, and J.M. Luber, Jr*. (SPON: P.M. Gootman) Long Island Jewish Medical Center, New Hyde Park, New York and IBM Instruments, Danbury, CT

Direct evidence for free radical (FR) production during aortic crossclamping and myocardial reperfusion (R) does not exist. Presence of FR were assessed in left ventricular myocardium (LV) of 1 month old swine (N=5) during cardiopulmonary bypass, pre cross clamp (C), with 30 min. of normothermic ischemia (I) and 10 min. (R). 100 mg LV biopsies were quick frozen in liquid $N_2$, transferred to cooled quartz tubes, and sealed with isopentane. Signal averaged spectra were measured at 100°K, 100 $KH_z$, 400μw power, with 5 Gauss modulation amplitude using an IBM ER/200D, X-band spectrometer. Three line EPR difference spectra (hyperfine splitting of 22 Gauss) between C and I, with the following characteristics (g), were noted:

| g | 2.015 | 2.002 | 1.988 |
|---|---|---|---|
| Intensity | 0.50 | 1.00 | 0.25 |

These signals disappear on warming to 200°K and cannot be regenerated. With R the differential spectrum disappears. This triplet signal represents an organic or $N_2$ based FR. Additional weak signals at g = 2.034 and 2.026 suggest Fe-S proteins. The FR signal may arise from $O_2$ reactions with proteins, lipids, and smaller species (ascorbate, tyrosine). Disappearance of the differential spectrum with reperfusion suggests that FR production occurs preferentially during ischemia.

55.6

ADENOSINE TRANSPORT IN CARDIAC SARCOLEMMAL VESICLES. Calvin C. Hale, Carol G. Carlton and Michael J. Povetto. Depts. of Biomedical Sci., Physio. and Dalton Res. Center, Univ. of MO, Columbia, MO 65211

Cardiac sarcolemmal (SL) vesicles (bovine) were prepared by differential and sucrose gradient centrifugation (J. Biochem. 91:1419-1426, 1982). SL vesicles were equilibrated in 160 mM NaCl, a 20 mM MOPS/TRIS pH 7.4. SL (1-3 mg/ml) vesicles were diluted 100-200 fold, into the same buffer containing 0.5 μM $^3$H-adenosine, and incubated at 37°C. The reaction was stopped at various times by dilution of incubates with 5 ml of ice cold 200 mM KCl, 20 mM MOPS/TRIS, 10mM EGTA, pH 7.4. Vesicles were immediately collected on glass fiber filters followed by 3 additional washes of the filter by stop solution. Adenosine accumulation into SL vesicles remained linear for approximately 30 minutes. Subsequent experiments utilized 20 minute incubations. Adenosine transport had an apparent Vmax of 0.81 pmoles adenosine/mg protein/sec and a Km of 7.3 μm. Adenosine transport was completely inhibited by 12 μM nitrobenzylthioinosine (NBMPR), $^3$H-NBMPR binding had a $K_D$ of 2.3 nM. In addition, adenosine transport activity was inactivated by two or more freeze-thaw cycles, sonication, or reconstitution protocols with Na cholate and Triton X-100 which reconstituted significant SL Na-Ca exchange activity into proteoliposomes. A partial cation and anion dependency was demonstrated. The overall levels of transport with various ions was as follows: Li>NaCl>KCl-> $KCH_4SO_4$ = choline Cl > mannitol. (Supported in part by NIH grant HL 27336).

56.1

AN IN VITRO MODEL OF PLATELET AGGREGATION IN STENOTIC ARTERIES
Deborah Morley* and William P. Santamore. Bowman Gray School of Medicine, Winston-Salem, NC 27103

Clinical and experimental evidence suggest a strong relation between arterial stenosis, platelet aggregation, and thrombus formation. To study platelet accumulation in stenotic arteries, we developed an in vitro model. A constant flow perfusion pump drives the perfusate through an arterial segment and a distal resistance in a recirculating pathway. All interconnections are made with silastic tubing. The system is pre-filled with divalent cation-free Tyrodes solution and (Indium-III) autologous platelets suspended in whole citrated blood are flowed. An external plastic constrictor applied to the artery provides a stenosis which is non-responsive to vasomotion. Proximal and distal pressures are monitored and the flow rate is computer controlled to maintain a constant proximal pressure. We exposed 6 arteries to flowing whole citrated blood at a proximal pressure of 100 mmHg for 15 minutes. In 3 arteries, the endothelium was intentionally damaged at the stenosis. Scanning electron microscopy demonstrated little platelet accumulation in stenotic arteries without endothelial damage. However, we observed extensive platelet aggregation in arteries with endothelial damage. Thus, this model can be used to investigate potential mechanisms of platelet aggregation under controlled hemodynamic conditions. Further, the model can allow both qualitative and quantitative evaluations of physiologic as well as pharmacologic determinants of platelet aggregation in stenotic arteries.

56.2

TRANSMURAL DISTRIBUTION OF MYOCARDIAL BLOOD FLOW DURING SELECTIVE CORONARY HEMODILUTION.
George J. Crystal. University of Illinois College of Medicine and Illinois Masonic Medical Center, Chicago, Illinois 60680

In 10 anesthetized, open chest dogs, the left anterior descending coronary artery (LAD) was cannulated and perfused with normal arterial blood or with arterial blood diluted with lactated Ringer's solution to an hematocrit 50% of control (HD). LAD perfusion pressure was set at 100 mmHg or at 50 mmHg to simulate coronary insufficiency (CI). Regional and mean myocardial blood flows (MBF) in LAD bed were measured with 15 μ radioactive microspheres.

| | CONTROL | HD | CI | HD-CI |
|---|---|---|---|---|
| MBF, ml/min/100g | 113 ±11 | 306* ±32 | 59* ±3 | 120 ±11 |
| ENDO/EPI RATIO | 1.15 ±0.10 | 1.30 ±0.10 | 0.76* ±0.04 | 0.73* ±0.06 |

Results are Mean ±SE. * P<0.05 from CONTROL.

HD caused substantial increase in MBF, which was uniform transmurally. CI reduced MBF and altered its transmural distribution (endo<epi). Combining HD with CI returned MBF to control level, although endo:epi flow gradient persisted. Because resistance vessels were maximally dilated during CI (no reactive hyperemia), doubling of MBF during HD-CI reflected significant contribution of reduced viscosity to increased myocardial perfusion during HD. (Supported by NIH Grant HL-33803)

56.3

Coronary response to exercise after ventricular sympathectomy.
P.A. Gwirtz, H.J. Mass, J.R. Strader*, C.E. Jones. Dept. of Physiology, Tex. Coll of Osteo Med., Fort Worth, Tx 76107.

We examined the effects of chronic sympathectomy on the relationships between left ventricular mechanical performance, (systolic pressure [LVSP], dP/dt max, LVSP-HR product, tension-time-index [TTI]), coronary blood flow and exercise workload in 9 chronically instrumented controls (C) and 7 dogs which had been sympathectomized 2 (S2) and 8 (S8) wk earlier. In each group the values at rest (R) and during exercise at 4 mph/12% grade (E) are shown (*p<0.05 vs C):

| | NS | | S2 | | S8 | |
|---|---|---|---|---|---|---|
| | R | E | R | E | R | E |
| LVSP (mmHg) | 139 ±4 | 171 ±7 | 120 ±8* | 131 ±7* | 117 ±11* | 140 ±13* |
| dP/dt max (mmHg/s) | 3796 ±387 | 7207 ±852 | 2885 ±344 | 4566 ±720 | 3149 ±297 | 5380 ±423 |
| HR (bpm) | 109 ±7 | 193 ±10 | 149 ±5* | 220 ±13* | 129 ±14* | 248 ±8* |
| LVSP.HR ($x10^3$) | 15.0 ±0.8 | 33.0 ±1.0 | 17.9 ±0.8 | 29.2 ±1.0 | 15.6 ±0.6 | 34.6 ±1.0 |
| TTI (mmHg.s/m) | 1474 ±142 | 2177 ±164 | 1945 ±135 | 2684 ±347 | 1339 ±238 | 2747 ±276 |
| CBF (ml/m/100g) | 65 ±7 | 88 ±13 | 65 ±6 | 77 ±9 | 34 ±3* | 50 ±10* |

Thus, there was an apparent progressive effect of sympathectomy on the coronary response to exercise, such that the relationship between ventricular performance and flow was significantly changed after 8 wk. (Supported by NIH HL-29232, HL-31144, and HL-31472.

56.4

ELECTRICAL STIMULATION INDUCED-RELAXATION OF CANINE CORONARY ARTERY: POSSIBLE INVOLVEMENT OF DOPAMINERGIC RECEPTOR.
M. Feletou and P.M. Vanhoutte, Department of Physiology and Biophysics, Mayo Clinic, Rochester, MN 55905.

Experiments were designed to determine the mechanism by which electrical stimulation causes tetrodotoxin-insensitive relaxation in canine coronary arteries. Rings of left anterior descending coronary arteries were suspended in organ chambers between platinum electrodes. Experiments were performed after treatment with phenoxybenzamine and in presence of propranolol. Electrical stimulation (3 Hz, 9V, 2 msec) causes relaxation which was more pronounced in distal than in proximal segments of the artery. Calcium-free solution and calcium-antagonists reduced the relaxation. 6-Hydroxydopamine induced a small inhibition of the relaxation induced by electrical stimulation; in the presence of pargyline it virtually abolished it. The non-selective dopaminergic antagonist droperidol and the selective $DA_1$ antagonist SKF R83566 (R-7-bromo-8-hydroxy-3-methyl-1 phenyl-2,3,4,5, tetrahydro-1-H-3-benzazepine) caused a concentration-dependent inhibition of the relaxation; the $DA_2$ antagonist domperidone was ineffective. These results suggest that electrical stimulation causes relaxation by liberating an endogenous vasodilator substance, presumably dopamine. (Supported in part by NIH grant HL 05883.)

56.5

CORONARY COLLATERAL FORMATION IN THE PONY: CUMMULATIVE EFFECTS OF TWO MINUTE CORONARY ARTERY OCCLUSIONS.
C. R. Ross,* K.S. Rugh,* R.D. Sarazan,* H. E. Garner, Dalton Research Center, University of Missouri, Columbia, MO 65211.

It has been shown that 2 min occlusions of the left anterior descending coronary artery (LAD) at ½ hr intervals, 8 hrs daily, 5 days a week, prompts the development of functionally adequate collateral perfusion in the conscious pony. Partial regression of collateral function is noted during the off intervals. The hypothesis that episodes of partial regression associated with this interrupted occlusion regimen increases the number of occlusions required to produce collateralization was tested by comparing results in animals subjected to an uninterrupted occlusion regimen, i.e., occlusions at ½ hr intervals around the clock. In these studies ponies were instrumented with a pneumatic occluder around the LAD and a crystal pair for measurement of myocardial segment shortening in the ischemic region. The end point for collateralization was defined as the time when segment shortening during occlusion had returned to 95% of control. Results:

| Group | n | Occlusions (X±SE) | Days (X±SE) |
|---|---|---|---|
| Interrupted Regimen | 9 | 378±73 | 38.0±7.9 |
| Uninterrupted Regimen | 8 | 496±49 | 13.6±1.9 |

The number of occlusions required for collateralization was not significantly different in the two groups (P>0.05). Thus, the hypothesis that repeated episodes of partial collateral regression increases the number of occlusions required for collateralization is not supported by this study.

56.6

INVERSE RELATIONSHIP BETWEEN REACTIVE HYPEREMIC CORONARY FLOW AND REGIONAL MYOCARDIAL SEGMENT SHORTENING IN THE CONSCIOUS PONY.
R.D. Sarazan,* C.R. Ross,* K.S. Rugh,* R.B. Boatwright,* D.O. Williams,* H.E. Garner, D.M. Griggs, Jr., Dalton Res. Center University of Missouri, Columbia, Missouri 65211

It has previously been shown in the dog that a characteristic overshoot in myocardial segment shortening (SS) during systole occurs with reactive hyperemia (RH) following release of a coronary artery occlusion. We studied the relationship between left anterior descending coronary artery (LAD) flow and SS in the LAD dependent region of chronically instrumented ponies. A commonly observed phenomenon quantitatively analyzed in 5 ponies revealed that SS was reduced during RH. The ponies were instrumented with a pneumatic occluder and Doppler flow probe on the LAD, a Konigsberg micromanometer in the left ventricular cavity and a pair of sonomicrometer crystals in the left ventricular free wall. Following the release of a 2 minute LAD occlusion, SS was reduced from 18.5±1.8% to 13.3±1.4% (28%) during peak RH flow velocity which was 337±-20% of control. As RH decreased, myocardial SS returned toward control levels. In one pony where RH flow was manually reduced to preocclusion levels, SS also returned to control. A regression of myocardial SS (% control) on hyperemic flow velocity (cm/sec) in these ponies demonstrated a significant (P<0.05) inverse linear relationship (slope = -0.643 to -0.179; r = 0.780 to 0.992. Thus under these experimental conditions there is a paradoxical reduction in myocardial SS with increased flow during RH in the pony.

56.7

XANTHINE OXIDASE IS DETECTED IN ISCHEMIC RAT HEART BUT NOT HUMAN HEARTS. Lynne Eddy, James Stewart*, Harold Jones*, Derek Yellon*, Joe McCord*, James Downey. Univ. South Alabama, Mobile, AL 36688, Vanderbilt Univ., Nashville, TN 37232 and St Thomas' Hospital, London, UK.

We have proposed that xanthine dehydrogenase (XD) is converted to xanthine oxidase (XO) in ischemia, becoming a source of toxic free radicals. We measured the time course of this conversion during total ischemia in rat and human ventricle. Rat hearts were subjected to 0,2,5,10,20 and 30 min of total ischemia at 37C. Samples from 4 human organ donors were subjected to 0 and 30 min of ischemia. All tissue was homogenized in ice cold phosphate buffer containing 1 mM PMSF and 10 mM dithioerythritol, spun at 100,000 xg for 30 min and the supernatant passed through a Sephadex G25 column. 0.2 ml of the enzyme rich fraction was added to two cuvettes each containing phosphate buffer (pH 7.8), 50 uM xanthine, and 0.3 mM NAD when required. Allopurinol was added to one cuvette which served as the blank. Urate production (absorbance at 295 nm) in the absence of NAD reflected XO activity while that in the presence of NAD reflected XO + XD. 1.3 +-.3 mU/g XO was present in control rat heart, increasing to 5.8+-1.5 mU/g after 5 min ischemia, and thereafter unchanged with 26% of the enzyme XO. Exogenous trypsin could not cause any further conversion. No XD or XO was detected in any human sample even when the assay fraction was concentrated 20x. We conclude that though XO may be a source of free radical in the rat heart, it is probably not in the human.

56.8

MODIFICATION OF THE FATTY ACYL COMPOSITION OF MYOCARDIAL PHOSPHOLIPIDS (PL): EFFECT ON ISCHEMIC DAMAGE. Carl E. Hock, Marie A. Holahan* and Diane K. Reibel. University of Medicine and Dentistry of New Jersey-SOM, Camden, NJ, 08103 and Thomas Jefferson University, Phila. PA, 19107.

Four weeks of feeding 5% menhaden oil (MO) to rats produced both profound changes in the fatty acyl composition of PL in myocardial membranes and a reduction ($p<0.05$) in the loss of creatine kinase following coronary artery ligation, compared to feeding 5% corn oil (CO). The MO diet did not significantly alter the content of total or individual PL in the heart. However, dietary MO resulted in significant elevations in the percent of the fatty acids in total PL that were saturated ($p<0.01$), the n-3/n-6 ratio ($p<0.001$) and the double bond index ($p<0.001$). The changes in total PL were not uniformly reflected in the individual PL (i.e., phosphatidylcholine - PC, phosphatidylethanolamine - PE, phosphatidylinositol - PI and cardiolipin - CL). The double bond index was not altered in PC but was significantly elevated in myocardial PE ($p<0.001$). The incorporation of arachidonic acid was significantly reduced ($p<0.001$) in PC and PE but was not significantly altered in either PI or CL with MO feeding. Furthermore, the n-3 fatty acids eicosapentaenoic (EPA) and docosahexaenoic acids were readily incorporated into PC, PE and CL but only EPA was incorporated into PI. Thus, 4 weeks of dietary MO resulted in selective alterations of individual myocardial PL. These membrane changes may be involved in the observed reduction of ischemic damage.

56.9

INTERACTION BETWEEN ADENOSINE AND ENDOTHELIUM DEPENDENT RELAXATION (EDRF) IN CANINE CORONARY ARTERIES. Shannon P. Williams* and S. Jamal Mustafa. Department of Pharmacology School of Medicine, East Carolina University, Greenville, NC 27834

The endothelium can cause vasodilation in response to various agents via EDRF. This study investigated the interaction between the endothelium and adenosine in producing relaxation of canine coronary arteries. Coronary artery rings (<1 mm o.d., 3 mm wide ) were mounted in isolated muscle baths containing oxygenated Krebs buffer, pH 7.4 (95% $O_2$ + 5% $CO_2$). After one hour equilibration (.5 g resting tension), the rings were precontracted with 30 mM KCl or $1x10^{-5}$M $PGF_{2\alpha}$. Our results show that, unlike the relaxation produced by adenosine ($1x10^{-5}$M), the endothelium dependent relaxation produced by acetylcholine ($1x10^{-5}$M) is not reversed with the addition of adenosine deaminase (.4 units/ml). Using the same preparation we were also able to show that mechanical removal of the endothelium in coronary artery reduces the relaxation produced by adenosine when precontracted with KCl but not with $PGF_{2\alpha}$. These findings suggest that adenosine is not an EDRF as was suggested by Deussen, Moser and Schrader (Purines: Pharmacology and Physiological Roles by T. W. Stone, p. 257, Pub: MacMillan, 1985); and that in coronary artery the endothelium and adenosine may interact to maintain vascular tone. (Supported by HL 27339)

56.10

RELEASE OF PROSTACYCLIN AND ENDOTHELIUM-DERIVED RELAXING FACTOR BY ACETYLCHOLINE FROM CANINE FEMORAL ARTERIES. E.L. Rubanyi*, G.M. Rubanyi, J.C. Romero and P.M. Vanhoutte. Dept. Physiology, Mayo Clinic, Rochester, MN 55905.

Acetylcholine (ACh) can stimulate the release of both prostacyclin ($PGI_2$) and a still unidentified endothelium-derived relaxing factor from vascular endothelial cells. To determine whether ACh stimulates the release of these two substances by a similar mechanism isolated segments of canine femoral artery with endothelium were perfused. The release of $PGI_2$ into the effluent was determined by radioimmunoassay and that of endothelium-derived relaxing factor by bioassay (superfused canine coronary artery ring without endothelium). Increasing concentrations ($10^{-8}$ to $10^{-6}$M) of ACh (infused upstream of the femoral artery) produced a biphasic concentration-relaxation curve in the bioassay rings [transient relaxation evoked by $10^{-8}$ to $10^{-7}$M ACh (first phase) and sustained relaxations by $2x10^{-7}$ to $10^{-6}$M ACh (second phase)]. The basal release of $PGI_2$ (67.5±14.6 pg/ml) was increased (more than ten-fold) only by higher concentrations of ACh ($10^{-7}$ to $10^{-6}$M). The relaxations were not significantly affected, but the release of $PGI_2$ prevented by indomethacin ($10^{-5}$M). These experiments suggest that only the second phase of the acetylcholine-induced release of endothelium-derived relaxing factor triggered by mechanism(s) which evoke the liberation of $PGI_2$.

56.11

ENTRAPMENT OF MICROSPHERES IN THE MYOCARDIUM IN RESPONSE TO SEVERE ANEMIA. D.K. Wilkerson*, A.L. Rosen, S.A. Gould*, L.R. Sehgal*, H.L. Sehgal*, and G.S. Moss*. Department of Surgery, Michael Reese Hospital & Medical Center, Chicago, Illinois.

Coronary arteries dilate in response to anemia. Radioactive microspheres (RM) can measure coronary blood flow during anemia if the RM undergo significant entrapment. We report on the % non-entrapment (% NE) of 9 micron, RM in hemodiluted primates. Aortic, left atrial(LA), and coronary sinus catheters were inserted into 14 anesthetized baboons. Baseline % NE was measured by the reference sample technique following LA injection of $2 \times 10^6$ RM. One group (N=7) was hemodiluted to a hematocrit (hct) of 5%, the other control group underwent a sham exchange. % NE at baseline (N=14) was 6.5 ± 3.5% (mean ± SD). % NE, as a function of hct, is given in the table for the two groups.

| | Hematocrit (%) | | |
|---|---|---|---|
| | 20 | 10 | 5 |
| Hemodiluted | 3.9 ± 3.3 | 6.8 ± 6.5 | 6.3 ± 8.2 |
| Control | 7.9 ± 3.5 | 10.3 ± 6.4 | 7.8 ± 5.9 |

There were no significant differences between these values and baseline. Conclusion: Nine micron RM undergo significant and constant entrapment in extreme anemia.

56.12

REGRESSION AND RECOVERY OF CORONARY COLLATERAL BLOOD FLOW AFTER AORTA-CORONARY BYPASS. Noriyasu Watanabe*, Shuji Yonekura*, Arthur G. Williams*, and H. Fred Downey. Tex. Coll. of Osteopath. Med., Ft. Worth, Texas 76107.

Closure and reopening of coronary collaterals during simulated aorta-coronary bypass was studied in four anesthetized dogs 8-9 weeks after LAD occlusion by surgically implanted ameroid constrictors. In an isolated, supported, beating heart preparation, the LAD was cannulated distal to the occlusion and perfused independently of the remainder of the coronary circulation, which was perfused retrogradely from the aorta. Peripheral coronary pressure (PCP) and retrograde flow (RF) were measured during brief occlusions of the bypass. Collateral flow (CF) was estimated as the increase in non-LAD coronary flow during bypass obstruction. Collateral resistance (CR) was computed from (perfusion pressure - PCP) / CF. Before bypass, PCP=79±3 mmHg, RF=64±12 ml/min, CF=27±9 ml/min, and CR=0.98±0.21 mmHg/ml/min. Bypass reperfusion of the LAD for 100 min significantly decreased PCP by 26%, RF by 46%, and CF by 39%, and significantly increased CR by 278%. Thirty minutes after discontinuing bypass, CR decreased from its maximum by 61%. These results demonstrate that chronically-induced coronary collaterals change their resistance to meet changing needs of their perfusion area. (Supported by HL-35027 and TCOM Faculty Research Grants).

56.13

NITROPRUSSIDE-INDUCED INHIBITION OF $PGF_{2\alpha}$ AND KCL-MEDIATED CONTRACTURES IN CANINE CORONARY VESSELS. D.V. DeFily, R.S. Keller, H.R. Adams, A.W. Jones and J.L. Parker, Dalton Res. Center; Depts. of Physiology and Veterinary Biomedical Sciences, University of Missouri, Columbia, 65211

Relaxation responses to nitroprusside (NP) were evaluated using large (1.70±.03 mm O.D.) and small (0.94±.05 mm O.D.) left circumflex coronary rings individually stretched to the apex of the length-tension relationship ($L_{max}$). $L_{max}$ averaged 190±5% and 156± 5% initial O.D. of large and small vessels respectively. Concentration-dependent isometric contractures to KCl (5-100 mM) and $PGF_{2\alpha}$ ($10^{-10}$-$3x10^{-5}$M) were determined prior to exposure to NP ($10^{-10}$-$10^{-4}$M). Much higher concentrations of NP were required to relax KCl contractures than $PGF_{2\alpha}$ at either equipotent or maximal concentrations of KCl and $PGF_{2\alpha}$. NP $IC_{50}$ values for $PGF_{2\alpha}$ vs. KCl contracted vessels averaged 44±9 vs. 570±140 nM for large vessels ($p<.01$) and 44±17 vs. 1360±480 nM ($p<.03$) for small vessels. Maximal NP relaxation ($10^{-4}$M) was greater with $PGF_{2\alpha}$- than with KCl-induced contractures in both large (109±14% vs 81±18%; $p<.05$) and small (111±17 vs 85±10%; $p<.05$) vessels. Results were unaffected in vascular rings with endothelium removed. Since NP was a less potent inhibitor of KCl depolarization contractures, we conclude that $Ca^{++}$ influx via membrane potential operated channels may be less readily inhibited by cGMP dependent mechanisms than influx via receptor operated events in coronary arteries.

## CELL BIOLOGY OF CULTURED CELLS

57.1

UPTAKE OF LYSOPHOSPHATIDES BY CARDIAC MYOCYTES S.P.Sedlis*, J.M. Sequeira*, N. El-Sherif. SUNY HEALTH SCIENCE AND VA MEDICAL CENTERS, BROOKLYN N.Y. 11209

To correlate lysophosphatidylcholine (LPC) mediated cytotoxicity with cellular incorporation of LPC we measured uptake and metabolism of $^{14}C$ LPC by cultured neonatal rat heart cells. Phospholipids were separated by HPLC. Uptake of LPC by cells superfused for 5 min with 10-100uM LPC was proportional to concentration. A 1 hour exposure to $\leq$ 80uM LPC did not damage cells, however a 10 min exposure to 100uM LPC was injurious (53% creatine kinase [CK] depletion and 53% trypan blue exclusion, $p<.01$). This difference could be explained in part by differences in metabolism. In 10 min 51% of 80 uM but only 24% of 100 uM LPC was metabolized ($p<.01$). Uptake of 80uM LPC reached plateau after 5 min (2.19+.13nM/mg prot.), however uptake of 100 uM LPC was 2.3+.18nM/mg prot. at 5 min and increased to 3.38+.57nM/mg prot. at 10 min ($p<.01$). Uptake during three succesive 5 min exposures to 100 uM LPC separated by 20 min recovery intervals resulted in greater uptake (5.34+.15nM/mg prot.) than after a single 10 min exposure ( $p<.01$), however there was no CK depletion or diminution in trypan blue exclusion. We conclude that metabolism as well as other mechanisms are responsible for the attenuation of damage sustained from LPC exposure.

57.2

SPONTANEOUS INCREASE OF GH AND PRL SECRETION BY PERIFUSED $GH_3$ CELLS. C.A.Lapp,* J.M. Tyler,* Y.S.Lee,* and M.E.Stachura. Medical College of GA and VA Medical Center, Augusta, GA 30910

$GH_3$ cell secretory behavior was studied in long-term (72 hr) perifusion to define observed fluctuations in GH and PRL production. Mechanically harvested cells ($1x10^7$ per column) were perifused at 4 ml/hr with Ham's F-10 medium containing 15% horse serum, 2.5% fetal calf serum, 100 units/ml penicillin and 100 ug/ml streptomycin. Routine behavior included a basal period of hormone secretion whose length varied (3-12 hrs), and was followed by steadily increasing secretion rates. Observed changes in cell number were not sufficient to account for increased secretion rates: a) there was no significant change in cell count after 72 hrs ($0.97 \pm 0.03x10^7$; n=18); b) maximum DNA increase was only 36% while GH secretion rose by 358% and PRL by 260%. Observed differences in length of basal secretion period, basal secretory rate, and magnitude of secretory rate increase were traced to several variables: 1) cells with identical lot and freeze numbers, but received at two different times, were different; 2) variability was a function of passage number (GH secretion decreased and PRL increased with increasing subculture number); 3) the presence of antifungal agents (e.g., nystatin or Fungizone) caused variations in secretory pattern (Clin Res 34:213A, 1986). Conclusions: 1) secretion of GH and PRL rises spontaneously in perifusion without a concomitant increase in $GH_3$ cell number; 2) $GH_3$ cell in vitro secretion is influenced by definable variables. (Supported by NIH #AM33388)

57.3

**DOG MASTOCYTOMA CELLS PRODUCE PELLET-ASSOCIATED PLATELET ACTIVATING FACTOR (PAF) AND LYSO-PAF.** **D.J. Elias*, F.H. Valone*, S.C. Lazarus*, W.M. Gold, Cardiovas. Res. Inst. and Dept. Medicine, Univ. Calif. San Francisco and V.A. Medical Ctr., San Francisco, CA 94143.**

**We have reported that PAF is produced by dog mastocytoma cells propagated in nude mice and is 1-O-alkyl-2-acetyl-sn-glycero-3-phosphorylcholine. In further studies using ionophore A23187 (0.1-1.0 μM), supernatants and pellets were extracted (modified Bligh and Dyer method). Samples were split, half were acetylated and all purified on silica gel G TLC plates in $CHCl_3$:MeOH:acetic acid:$H_2O$ (v/v 50:25:8:4), and PAF quantitated by rabbit platelet aggregation. The difference between acetylated and nonacetylated samples=lysoPAF. PAF (3 pmoles/$25x10^6$ cells) and lysoPAF (8 pmoles/$25x10^6$ cells) production peaked at 2 min, increased in a dose-dependent manner, and was primarily pellet-associated. Unstimulated pellets had no PAF and only 1 pmole lysoPAF/$25x10^6$ cells. Cells were incubated with [$^3$H]PAF (1 pmole), extracted and analyzed on HPLC. [$^3$H]PAF was metabolized to alkyl-acyl-GPC and not to lysoPAF. Conclusions: PAF production is pellet-associated, suggesting inhibited release or implicating PAF as an intracellular mediator. LysoPAF probably represents precursor rather than degradation product. The large amounts of lysoPAF compared to PAF suggest acetylation of lysoPAF to PAF is rate-limiting, inhibited or defective in these dog mastocytoma cells. (Supported in part by NHLBI HL-24136.)**

57.4

INDUCTION OF ALKALINE PHOSPHATASE IN HL-60 CELLS BY RETINOIC ACID. Deborah A. Swartz*, Malford E. Cullum and Maija H. Zile. Michigan State University, East Lansing, MI 48824

Vitamin A is involved in normal proliferation and differentiation of cells of ectodermal, mesodermal and endodermal origin. Retinoic acid, a physiological metabolite of vitamin A, is a potent differentiating agent and alters proliferation and differentiation of haemopoietic cells. The proliferation of the promyelocytic leukemia HL-60 cells is inhibited by retinoic acid and they are induced to differentiate into granulocytes. This terminal differentiation is accompanied by an increase in tissue transglutaminase and decrease in levels of expression of protooncogene c-myc. In other cell systems retinoic acid induces alkaline phosphatase. We now report the induction of alkaline phosphatase by retinoic acid in HL-60 cells. HL-60 cells, 4 x $10^5$ cells/ml, were exposed to $10^{-6}$M retinoic acid for 0, 1, 12, 24 and 36 hours. Control cells and retinoic acid treated cells were harvested at indicated times, the cell number and alkaline phosphatase determined. Differentiation was assessed by NBT dye reduction. Alkaline phosphatase activity was found to be increased after an incubation with retinoic acid, with a peak at 12 hours; thereafter it remained elevated. The increase in alkaline phosphatase activity was proportional to induction of differentiation by retinoic acid. Alkaline phosphatase induction may be a useful marker for retinoic acid induced differentiation of HL-60 cells. Supported in part by USDA 84-CRCR-1-1377.

57.5

ISOLATION, CHARACTERIZATION, AND LONG TERM CULTURE OF FETAL BOVINE TRACHEAL EPITHELIAL CELLS. Brenda L. Schumann* and George D. Leikauf* (SPON: G. P. Cooper). Univ. of Cincinnati, Cincinnati, OH 45267

Our objective was to establish long term cultures of tracheal epithelial cells for use in physiological studies. Epithelial cells were isolated by exposing and stripping the mucosal epithelium from the collagenous basement membrane. The tissue was minced and dissociated in Ca/Mg free medium containing 2% Dispase and 5mM dithiothreitol. Initially the cells were plated in a 1:1 mixture of Dulbecco's modified Eagle's medium (DMEM) and Ham's F12 with 10% fetal bovine serum (FBS). Fibroblasts were removed by selective trypsinization. On untreated plastic the plating efficiency was 23% with a doubling time of 22 h. and dome formation, a physiological characteristic of epithelial cells, was common. A comparative study of cell growth on different substrates showed that confluency was reached in 5 days on untreated plastic, 7 days on collagen-coated plastic and 10 days on Egelbreth-Holm Swarm mouse sarcoma matrix (EHS) coated plastic. Grown on EHS the cells exhibited a three dimensional organization, on untreated plastic they had a flattened configuration. Electron microscopy showed microvillous membranes with glycocalyx, and numerous desmosomes with tonofilaments. Immunohistochemical staining of keratin filaments was positive. The cells have been passaged over 20 times while still retaining their epithelioid characteristics.

57.6

GROWTH OF DOG COLONIC MUCOSA TRANSPLANTED INTO NUDE MICE. Marilyn S. Branton*, Robert M. Beazley*, and James B.Heneghan, Department of Surgery, Louisiana State University School of Medicine, New Orleans, Louisiana, 70112.

To improve the technique for transplantation of intestinal mucosal xenografts, the canine colonic mucosa was isolated by EDTA perfusion of the intact mesentery and by dissection from smooth muscle. The mucosal tissue was rinsed in media with antibiotics, incubated in vitro for 1 hr or 24 hrs at 37°C and transplanted into nude mice. Mucosal tissues isolated by dissection were placed subcutaneously (SubQ) with a covering membrane filter. EDTA isolated mucosal cells (EDTA) were placed at various sites or sealed inside membrane filter chambers. The number of animals in each group were: dissected mucosa placed SubQ in both flanks with filter: 20 mice; EDTA: 20 - SubQ without filter, 20 - SubQ with filter, 20 - intramuscular (IM) both thighs, 20 - intraperitoneal (IP): 10 - direct, 10 - in filter chambers. At 2,4,6, & 10 days, and 2,4,6,8,12 & 18 wks after implantation, the animals were sacrificed and the grafts were examined by light microscopy. The dissected SubQ & the EDTA IM grafts had the greatest viability. Filter paper increased the vascularity around the grafts. Viable enterocytes were seen in grafts examined after 2-21 days growth in vivo and after 3 to 6 weeks with 11/14 or 78.6% of the transplanted grafts surviving. Establishment of a baseline of successful growth of xenografted enterocytes will greatly increase the speed of the development of this technique. (Supported by American Cancer Society Grant PDT - 223).

57.7

THE IMMORTALIZATION OF SKELETAL MUSCLE MYOBLAST CELLS. M.Planas-Silva* and M.T. Crow. Dept. Biology, University of Houston-University Park, Houston, Texas 77004

We have introduced DNA encoding one of two nuclear oncogene constructs into primary muscle cell cultures from the embryonic chicken and rat in an attempt to establish stable cell lines representing the different skeletal muscle myoblast types in these tissues. The constructs used in these experiments were 1) pSVc-myc, which contains a genomic fragment of the mouse c-myc gene spanning the two 3'-most exons under the control of an SV40 promoter, and 2) pRSV-1609, which contains the gene encoding a temperature-sensitive SV40 large T antigen under the strong promoter action of the Rous sarcoma virus long terminal repeat. Each oncogene constructs was co-transfected into primary myoblast cultures along with pRSV-neo, a plasmid which confers geneticin (G418)-resistance to eucaryotic cells. Following passage to low cell densities, G418-resistant colonies were isolated and characterized. Expression of either oncogene construct rescued both the chicken and rat cultures from senescence. In both the rat and the chicken, clones containing the temperature-sensitive SV40 large T antigen exhibited varying degrees of muscle differentiation, with myotube formation being greatest at the nonpermissive temperature (41°C).

57.8

**CARBOHYDRATE SPECIFIC STRUCTURES OF BLOOD GROUP Ii ANTIGENS IN BREAST CARCINOMA IN WOMAN.** **Volker E. Dube*, Patricia Kallio*, Max Haid*, Anwar A. Hakim. Evanston Hospital, Evanston, Il. 60201**

**Tumor cells elaborate and release into the circulation a variety of tumor markers. Amongst these markers are the structures specific for the blood group Ii antigens, which are incompletely converted to ABH antigens on the membranes of tumor cells (Dube, et al. Mol. Immunol. 23:217-220, 1986). The I antigens in the sera of 67 woman with Breast Carcinoma (BCa), 58 with Benign Breast Disease (BBD) and 47 controls were measured by an Enzyme-Linked-Immunosorbent Assay (ELISA). In this assay, I antigen from ovarian cyst mucin was bound to the wells of polystyrene microtiter plates. The monoclonal human Anti-I antibody (Hy) was added to the wells followed by perchloric acid extracts of BCa and control sera at five different dilutions. The Anti-I binding to the solid phase I antigen was determined after incubation steps with peroxidase labelled anti-human IgM and substrate. The amount of BCa and control sera extracts giving 50% inhibition of Anti-I (Hy) binding was determined from the inhibition curves which were corrected by integrating the slope values into that of the standard curve of pooled normal serum. The I antigens were significantly higher in Pathologic Stage (PS) IV sera ($p<0.001$) and comparable in PS I, PS II, and PS III sera to those of BBD and control sera. The Anti-I (Hy) strongly bound Gal 1,4 GlcNAc 1,6 Gal (αGalNAc), Gal 1,4 GlcNAc 1,6 (Gal 1,4 GlcNAc 1,3) Gal and to a lesser entent (Gal 1,4 GlcNAc 1,3)$_2$, 0.06 0.09 and 0.35 mM giving 50% inhibition, respectively. It was concluded that similar structures may be expressed on the membrane of those clones of BCa cells that metastasize to sites in the body that are distant from the primary tumor, supporting a role of these carbohydrate structures in breast carcinoma cell metastasis. (Supported by PHS Grant No. CA 38878).**

## METABOLISM

58.1

**GLUCOSE OXIDATION BY ISOLATED GLOMERULI OF DIABETIC RATS.** **S.Feske*, R. Cordero* & A. McCall. Univ. Hosp.,Boston,MA.02118**

**Diabetes (DM) suppresses glucose oxidation by isolated cerebral microvessels and renal cortical slices. To evaluate the effect of diabetes on a specific tissue known to be susceptible to microvascular disease, we measured the in vitro oxidation of D-[U-14C]glucose to CO2 in isolated glomeruli from rats. To separate hyperglycemic from insulin effects, we compared rats from four groups:1) normal(N), 2)streptozotocin diabetics(D), 3)insulin-treated, diabetic rats(I), and 4)sucrose-fed,insulin-treated, diabetic rats(S). This last groups had marked hyperglycemia despite insulin treatment. We also measured total renal mass in each group. Mean group blood glucose levels (mg/dl) were 162±5(N),512±23(D),234±55(I) and 516±54(S). Glucose oxidation(nmol CO2/mg glomerular protein ± SE) was depressed by 35% in diabetic rats [22.8±1.6(N), 14.7±1.1(D)]. Insulin treatment corrected oxidation to normal in separate trials [19.3±1.3(N), 14.2±.8(D), 18.4±1(I)]. Sucrose feeding suppressed glucose oxidation by 44%, a change similar to that in untreated diabetics [9.1±.7(N), 5.1±.6(S)]. Untreated diabetes increased the ratio (times 100) of renal mass/body mass by 21% [.88±.03(N),1.11±.03(D)] but it was not changed in insulin-treated[.85±.02(I)] or sucrose-fed [.92±.08(S)] groups. We conclude that diabetes suppresses glucose oxidation in rat glomeruli and that this metabolic effect is more closely linked to hyperglycemia than to insulin availability. Finally, features of diabetes other than hyperglycemia may contribute to the renal enlargement of DM.**

58.2

FUEL OXIDATION IN MALNOURISHED EMPHYSEMA AND CANCER PATIENTS. SA Goldstein*, DH Elwyn*, J Askanazi, JM Kinney* Columbia University, New York, N.Y. 10032

Malnourished emphysema (Emph, n=11), cancer (Ca, n=4) and control (Cntl, n=4) patients (pts) were infused (either enterally or parenterally) with 5% dextrose ($D_5W$) for 36 hours and then assigned to either a 53% carbohydrate diet (CHO) or 55% fat diet, maintaining protein intake constant at 17% of the calories. The alternate diet was given the following week. Intake was set at 1.7 times resting energy expenditure (REE).

| | CHO Oxidation | | Kcal/REE | Fat Oxidation | | |
|---|---|---|---|---|---|---|
| X±SE | EMPH | CNTL | CA | EMPH | CNTL | CA |
| $D_5W$ | .40±.03 | .19±.09* | .26±.08* | .48±.04 | .72±.08* | .57±.05 |
| 53% CHO | .76±.02 | .71±.02* | .77±.01 | .04±.01 | .10±.04* | .02±.01# |
| 55% FAT | .42±.04 | .27±.06* | .44±.05 | .37±.05 | .54±.05* | .33±.03# |

* $p < 0.05$ compared to Emph; # $p < 0.05$ compared to Cntrl

Values of REE were highest in Emph pts, second highest in Ca pts and lowest in Cntl pts. Emph pts have a higher CHO oxidation and lower fat oxidation than Cntl pts. Values of CHO and fat oxidation in Ca pts were usually closer to those of Emph pts than Cntl pts. Ca pts had significantly higher rates of protein oxidation than Cntl or Emph pts. The Emph pts not only burn a greater amount of fuel, but also oxidize more CHO and less fat than Cntl pts. This is in the opposite direction to that seen in trauma or sepsis. Ca pts are at greatest risk of catabolizing excess lean body mass.

58.3

EFFECTS OF ACETAZOLAMIDE ON MUSCLE IONS AND METABOLITES DURING WORK OF LOW AND MODERATE INTENSITY. G.J.F. Heigenhauser, R.S. McKelvie*, M. Lindinger*. McMaster Health Sciences Centre, Hamilton, Ontario L8N 3Z5, Canada

We tested the hypothesis that during heavy exercise, compared to control conditions, with acetazolamide (ACZ) treatment the reduced plasma lactate ([La-]) is due to impaired La- production and release from exercising muscle. Following saline (SAL) or ACZ infusion, 4 healthy males exercised on a cycle ergometer for 6 min at 300 kpm, followed by 6 min at 75-80% $\dot{V}O_2$ max. Arterial blood and muscle biopsies were obtained 30 min after infusion at rest and during each workload. Compared to SAL at the end of the high workload plasma La- was reduced by 25% with ACZ. At the end of the high workload muscle La- was higher and glycogen utilization reduced in ACZ compared to SAL. At the high workload exercise associated increases in intracellular Na+ and Cl- were greater with the ACZ than in SAL, while intracellular K+ decreased less with ACZ. We confirmed our hypothesis that the reduced arterial La- during exercise following ACZ infusion is due both to impaired release of La- from muscle and reduced rate of glycolysis.

Supported by the Ontario Heart and Stroke Foundation and the Medical Research Council of Canada.

58.4

DEFECTIVE CHYLOMICRON REMOVAL ASSOCIATED WITH DEFECTIVE HEPARAN SULFATE METABOLISM IN NEPHROTIC RATS. James M. Felts and Ilona Staprans*. Univ. of Calif. and VA Medical Center, San Francisco, CA 94121.

Hyperlipemia is associated with the nephrotic syndrome in man and in nephrotic rat models. In the rat model we have shown that the rate of removal of injected radiolabeled chylomicrons is markedly slower ($T_{\frac{1}{2}}$=16min) compared to control rats ($T_{\frac{1}{2}}$=8min). We have also shown that urinary excretion of high charge glycosaminoglycans (GAGs) is markedly reduced in nephrotic rats compared to control rats. One of the GAGs, heparan sulfate (HS), is an effective cofactor in stimulating the lipoprotein lipase (LPL) reaction in vitro. Urinary excretion of HS is reduced from 123 nmoles/24hr to undetectable levels in nephrotic rats. The incorporation of injected $^{35}S$ into plasma HS was also markedly reduced in nephrotic rats. HS is possibly involved in vivo with the LPL enzyme system which is concerned with chylomicron clearance. We have isolated a highly purified form of HS from urine. Injection of this HS immediately restored the chylomicron removal rate to normal in nephrotic rats. The dosage used did not release soluble LPL into the circulation. A log-dose relationship was established between HS and chylomicron removal rates. Thus, one of the contributing factors to the hyperlipemia of nephrosis may be a reduced availability of HS at the LPL enzyme site leading to an accumulation of chylomicrons and very low density lipoproteins in plasma.

58.5

FLUORESCENT DERIVATIZATION OF SULFIDOPEPTIDE LEUKOTRIENES BY REACTION WITH O-PHTHALALDEHYDE AND SEPARATION BY HPLC. R. T. Dobrowsky*, G. O'Sullivan*, L. M. Ballas*, L. N. Fleisher*, N. C. Olson* (Spon: C. E. Stevens). North Carolina State University, Raleigh, NC 27606.

The presence of leukotrienes in biologic fluids is often detected by RIA and HPLC techniques. However, ultraviolet (UV) absorption lacks optimal sensitivity while RIA suffers from a degree of cross-reactivity with other eicosanoids. We hypothesized that detection of sulfidopeptide leukotrienes (i.e., $LTC_4$, $LTD_4$, $LTE_4$) might be enhanced by the formation of highly fluorescent substituted isoindoles by reaction of the primary amine of $LTC_4$, $LTD_4$, and $LTE_4$ with O-phthalaldehyde (OPA). Separation of the fluorescent derivatives was achieved by RP-HPLC in less than 30 minutes using a convex gradient of methanol- 50mM Na acetate-5% tetrahydrofuran pH 5.5. Detection limits realized under the conditions described were 0.35 ng, 3.8 ng, and 3.9 ng for $LTC_4$, $LTD_4$ and $LTE_4$, respectively, and represented an increased sensitivity over detection of these metabolites by UV spectroscopy. The method was applied to the detection of $LTC_4$ generated by zymosan stimulated murine peritoneal macrophages. RP-HPLC of the extract showed 25% of the total radioactivity migrating as authentic $LTC_4$; treating the extract with gamma-glutamyltranspeptidase decreased the initial fluorescence by 66% providing further confirmation of the authenticity of the $LTC_4$-OPA derivative. Supported by NIH HL32726.

58.6

PROSTACYCLIN PRODUCTION BY HUMAN RHABDOSARCOMA CELLS. G. L. Longenecker and B. J. Beyers*, Pharmacology, Univ. South Alabama, Mobile, AL 36688.

Tumor cells (TC) may produce thromboxane (TX) and/or prostacyclin (PGI). TC also cause platelet aggregation (PA), which may be involved in successful TC metastasis. Human rhabdosarcoma (RD) cells cause PA by a mechanism(s) involving ADP and TX, and sensitive to inhibition by PGI. Production of PGI and TX by RD was studied to ascertain potential involvement in RD-PA. RD were grown in layers in medium 199, and were used as layers or suspensions (50 million/ml, from layers by treatment with calcium free medium, $\leq$ 15 min). AA (20 uM, final) was added to the HBSS media and aliquots were taken at fixed times. Suspension aliquots were treated with indomethacin (5 ug/ml, final) and made cell free by centrifugation (16,000 x g, 5 min, 4 C). RIA of the aliquots indicated time-dependent production of PGI by RD: layers produced $\leq$25 pg, and suspensions $\leq$100 pg, per 10 million RD. PGI production plateaued at 10 minutes for suspensions and at 15 minutes for layers. TX production was below limits of detection. Thus, RD-TC, which cause PA, produce significant amounts of an anti-PA compound: interference with RD PGI production could enhance RD-PA and possibly RD metastasis. Grant 0092, Smokeless Tobacco Research Council.

58.7

WHOLE-BODY CHOLESTEROL TURNOVER IN LEAN AND OBESE ZUCKER RATS. A.D. Hartman. L.S.U. Medical Center, New Orleans, La. 70119.

The genetically obese Zucker rat, like it's human counterpart, is hypercholesterolemic. The objective of this study was to determine if the obese Zucker rat shares the same perturbations in whole-body cholesterol turnover as obese humans. Chow-fed lean and obese Zucker rats were injected intravenously with a suspension of $^{14}C$-cholesterol in 0.9% saline. Tail vein blood samples were obtained several times a wk for the first three wk and at weekly intervals thereafter for up to 3 mo. Cholesterol specific activity-time curves for both groups demonstrated biexponential decay. Fractional removal rates calculated for both exponentials were decreased significantly in obese animals. Kinetic analysis based on a two-compartment system, revealed non-significant increases in the sizes of pools A and B in the obese rats. Cholesterol removal from pool A was significantly reduced in obese rats due to a decreased rate of transfer to pool B. These data suggest that the obese Zucker rat exhibits a decreased rate of biliary excretion of cholesterol rather than an increased cholesterol production rate as in obese humans. (Supported in part by a BRSG grant from LSU Med. Ctr. and a grant from the Am. Heart Assoc. La., Inc.)

58.8

GLUCOSAMINE-ACETOACETATE CONDENSATE: ethyl-2-methyl-5(D-arabinotetrahydroxybutyl)-pyrrole carboxylate; ITS EFFECT UPON BOUND CARBOHYDRATES IN SERUM AND TISSUE OF BORN DIABETIC MICE. Jorge L. Padron, Drury College, Springfield, Mo. 65802

Pyrrole Condensate(PC) a condensation product of D-glucosamine and acetoacetate has been isolated from human diabetic urine and causes significant increases in the plasma insulin levels of white albino rats. Recently we have determined that it causes changes in the levels of blood sugar, plasma insulin and liver glycogen of born diabetic mice(C57BLKs-db) toward values normally found in the normal mice. Similar results were shown for the bound serum levels of hexose, hexosamine and uronic acids. The levels of glycosaminoglycans measured as uronic acid content, were increased in the diabetic mice and restored to nearly normal levels by the action of (PC). The treatment consisted of a 2% solution orally administered during a period of 28 days as a sole source of water intake. Hexuronic acid was determined by the modified carbazole method of Bitter and Muir. The anthrone reaction was used for the determination of bound hexoses. Hexosamine was determined by a modification of the Elson-Morgan method. The glycosaminoglycans from trachea cartilage were extracted with 3.0 M $MgCl_2$ for a period of 48 hours, and the uronic acid and protein content measured. It has been reported in the literature that drug induced diabetes leads to significant changes in the levels of tissue proteoglycans and that insulin normalizes the process. We suggest that a role of (PC) could be the stimulation of insulin synthesis.

58.9

EFFECT OF SOMATOSTATIN ON CARDIAC OUTPUT MEASUREMENTS. D. W. O'Brien*, C. T. Kappagoda, R. V. Rajotte*, G. D. Molnar* and K. Toth*. Muttart Diabetes Research and Training Center, University of Alberta, Edmonton, Alberta, T6G 2N8, Canada.

Hepatic insulin extraction (HIE) may be estimated from peripheral insulin, and hepatic blood flow estimated as a fixed percentage of cardiac output (CO). Somatostatin has been used to suppress endogenous insulin during the measurement of HIE. In anesthetized dogs the effect of somatostatin on cardiac output was measured simultaneously by the Fick method and by noninvasive impedance cardiography. No significant difference was found between the measurement of CO by impedance cardiography, and the Fick technique ($p > 0.05$, n=6). During a 45 min infusion of somatostatin 800 $ng.kg^{-1}.min^{-1}$, CO was not significantly affected. Heart rate was unchanged at 134 ± 16 b/min ($\bar{X}$ ± SEM), whereas stroke volume decreased 1.14 ± 0.14 $mls.kg^{-1}.min^{-1}$ to 1.01 ± 0.05 ($\bar{X}$ ± SEM) (N.S.) with the result that CO was unchanged. During the same period peripheral insulin fell from 6.7 ± 1.8 mU/L to 0.76 ± 0.1 ($p < 0.02$, n=6). These results suggest that impedance cardiography may be used to estimate CO in noninvasive clinical studies of HIE, and that while somatostatin may be infused simultaneously to suppress endogenous insulin in these studies, the cardiac output remains unaffected.

58.10

**EXPERIMENTAL STUDIES OF HUMAN KELOIDS AND HYPERTROPHIC SCARS UTILIZING ATHYMIC NUDE MICE.** **M.R. Shetlar, C.L. Shetlar*. Department of Dermatology and Biochemistry, Health Sciences Center and Department of Food and Nutrition, Texas Tech University, Lubbock, TX 79430, and C.W. Kischer*, Department of Anatomy, University of Arizona Health Sciences Center, Tucson, AZ 85724.**

**Thirty different human keloids or hypertrophic scars have been maintained in athymic nude mice for periods of time varying from 14 days to 180 days. In most cases, the implanted tissue did not change morphologically as indicated by light microscopy or by alterations in the glycosaminoglycans. In a few cases, when the keloid had been treated with steroids before removal and implantation in mice, there were changes both in morphologic appearance and in glycosaminoglycan distribution. It appears that the use of implants of human keloid and hypertrophic scar tissue in athymic nude mice has merit as a model for research on development and treatment under controlled conditions.** **(Supported in part by NIH GM34928)**

58.11

DIPEPTIDYL PEPTIDASE II IN ASTROGLIAL CELLS CULTURED FROM NEONATAL RAT BRAIN. B.R. Stevens, M. Raizada, C. Sumners, A. Fernandez, & L. Rech. Univ. Florida, College of Medicine, Dept. of Physiology, Gainesville, FL 32610.

Astroglial cells in primary culture from neonatal rat brain display prominent dipeptidyl peptidase II (DPP-II) activity. This amino exopeptidase cleaves off selected dipeptides (e.g., gly-pro) from peptides which contain N-terminal penultimate prolyl residues (i.e., gly-pro-R). Glial cells in primary culture were prepared by the method of Clark et al (JBC 259(1984):11672); the cultures contained >95% astrocytic glial cells. DPP-II activity was assayed using glycylproline-p-nitroanilide (GPN) substrate in acetate buffer pH 5.4. The hydrolytic release of gly-pro plus p-nitroanilide was monitored in real-time spectrophotometrically, or alternatively by our novel mercury-stop technique. At its optimal pH=5.4, brain glial DPP-II activity dominated (99%+) over other amino-exopeptidases. At pH>8, DPP-II activity was 98% inhibited. DPP-IV activity was essentially absent. DPP-II was inhibited 95% by 10 μM $HgCl_2$, but redox sulhydryl agents were without effect. K+ ion was mildly inhibitory. Chelators were not inhibitory. PMSF and puromycin were partially inhibitory. These data are consistent with DPP-II properties associated with whole brain and also non-brain tissues. Supported by NIH grant AM36567.

58.12

IN VIVO RENAL VIABILITY ASSESSMENT BY $^{31}P$ MAGNETIC RESONANCE SPECTROSCOPY (MRS) IN AN EXTERIORIZED KIDNEY TRANSPLANT MODEL. N.T. Stowe, W.J. MacIntyre*, J. Jojima*, T.C. Ng*, A.W. Majors*, H.A. Rolin*, M.O. Magnusson*, A.C. Novick*, T.F. Meaney* Cleveland Clinic Foundation, Cleveland, Ohio

Viability determinations of kidneys previously attempted by us with proton imaging have been extended to $^{31}P$ MRS to study the relationship between total adenine nucleotide (TAN) levels, intracellular pH and renal viability. The primary difficulty in obtaining useful $^{31}P$ spectra of the kidney using surface coils without depth selectivity is the presence of signals generated by extra-renal tissue. This problem was minimized by transplanting the kidney to the neck of an animal. The purpose of this study was to develop an in vivo technique of transplanting a dog kidney to the neck of a dog to test $^{31}P$ MRS evaluation of renal viability. The $^{31}P$ MRS spectra were obtained on a 1.4T imager. Spectra obtained from kidneys not subjected to ischemia, identified three individual phosphorous nuclei of ATP, and the inorganic phosphate peak, Pi. During occlusion of the renal artery for 30 min., serial measurements of the $^{31}P$ spectra showed a reduction in the three ATP peaks with an increase in the Pi peak and a drop in pH. Upon reperfusion, pH and ATP levels returned to control levels within 14 min. TAN levels were also verified by HPLC. These studies obtained with a conventional MRI system demonstrate a practical means of assessing TAN levels and pH changes which may reflect renal viability.

## SHOCK

59.1

**HEMORRHAGIC SHOCK IN CECECTOMIZED GERMFREE RATS.** **James B. Heneghan. Department of Physiology, Louisiana State University School of Medicine, New Orleans, Louisiana, 70112.**

**Many current models of septic shock in conventional (CV) rats utilize cecal ligation and perforation. To determine the influence of the germfree (GF) rat's enlarged cecum on its response to hemorrhagic shock, 10 litters of 8 germfree rats each were divided randomly into 4 groups: 2 CV control, 2 GF control, 2 CV cecectomized, and 2 GF cecectomized. Littermates were conventionalized (exposed to a "normal" flora at 4 weeks of age, cecectomized at 7 weeks, and bled at 14 weeks. Under methoxyflurane anesthesia, the rats were cannulated (femoral artery), heparinized, restrained, and allowed to awaken. Blood pressure was maintained at 60 mm Hg for 1 hr and at 50 mm Hg for 3 hrs, by adjusting the burette reservoir. In the GF cecectomized rats, 95% (19/20) survived but only 50% (10/20) of the other 3 categories did. Cecectomized GF rats required 3% of their shed blood; the other 3 groups needed 10-15%. The presence in the GF rat cecum of a 5 times greater quantity of bioactive and vasoactive substances than in the CV cecum may cause these changes in basic cardiovascular parameters in control GF rats: decreased cardiac output, blood volume, heart weight, & vasoconstriction to epinephrine in the mesenteric vessels, plus increased hemoconcentration and blood viscosity. In cecectomized GF rats, these parameters return to the CV levels and help to protect during the hypovolemic trauma. Clearly, the rat's cecum may produce significant cardiovascular effects during trauma or stress.**

59.2

CHRONOTROPIC ACTIONS OF ISOBUTYLMETHYLXANTHINE IN EARLY SEPSIS Lani W. Smith, Stephen L. Winbery*, L. Allen Barker*, and Kathleen H. McDonough, Depts. of Physiology and Pharmacology, L.S.U. Medical Center, New Orleans, LA 70112.

Right atria obtained from rats in early sepsis show a supersensitivity to the chronotropic actions of β-agonists. To determine if this supersensitivity was due to an alteration in phosphodiesterase activity, the chronotropic actions of isobutylmethylxanthine (IBMX) were studied in right atria (RA) obtained from rats 24 hr after cecal ligation and puncture (CP) or sham surgery (SH). RA were suspended in Krebs-Henseleit bicarbonate buffer at 33° C and cumulative dose-response curves for IBMX or isoproterenol (ISO) in the presence of 15 or 50 nM IBMX were constructed. Atrial rates prior to IBMX or ISO stimulation were significantly elevated in tissues from CP rats, but there was no difference in the maximal atrial rate observed with IBMX or ISO stimulation. No differences were observed between the $EC_{50}$ values for the chronotropic actions of IBMX on RA obtained from CP and SH rats. Furthermore, no differences were observed between the $EC_{50}$ values for ISO in the presence of either 15 or 50 nM IBMX. These results suggest that the supersensitivity seen for the chronotropic actions of β-agonists on RA from CP rats is not due to alterations in phosphodiesterase activity. (Supported by NIH grants HL 32749 and NU05804 and by a grant from the Ileitis and Colitis Foundation)

59.3

CARDIOVASCULAR COMPENSATION TO HEMORRHAGE (H) MAY BE AUGMENTED BY LIPOXYGENASE INHIBITION. Gerald Johnson III, and Robert F. Bond. Oral Roberts University, School of Medicine, Tulsa, OK 74171.

The arachidonic acid (AA) cascade has been implicated in the response to H. The two primary metabolic pathways for AA are: 1) the lipoxygenase pathway to leukotrienes, and 2) the cyclooxygenase pathway to prostacyclin, thromboxane $A_2$ and prostaglandins. The purpose of this study was to determine if the response to H is altered by the lipoxygenase inhibitor propyl gallate. Each experiment utilized two pentobarbitalized Sprague-Dawley rats. The experimental rats received 1 mg/kg/hr iv propyl gallate while the control rats were infused with a similar volume of vehicle. Both were simultaneously bled into calibrated burets to 60 then 30 mmHg MAP. The 30 mmHg was maintained until 20% uptake at which time they were reinfused and observed for an additional 2 hours. RESULTS: The dose of propyl gallate used produced no alteration in 1) MAP (123 ± 8 vs 124 ± 6 mmHg), 2) compensation times (100 ± 4 vs 85 ± 8 min), 3) decompensation times (70 ± 5 vs 61 ± 9 min) or 4) total times (170 ± 8 vs 147 ± 16 min) in control and experimental rats. The max blood loss, however, was greater ($P<.02$) for the propyl gallate treated (28.5 ± .8 ml/kg) than controls (26.2 ± .6 ml/kg) suggesting that these rats were able to compensate by more intensely reducing their intravascular capacity in response to H.

Supported in part by American Heart Association, Oklahoma Affiliate, Inc.

59.4

THE INFLUENCE OF CYCLOOXYGENASE INHIBITION (CI) ON CARDIOVASCULAR RESPONSE TO HEMORRHAGE (H). Robert F. Bond and Gerald Johnson, III. Oral Roberts University School of Medicine, Tulsa, OK 74171.

Previous studies from this laboratory have suggested that the CI Na meclofenamate (NM) reduces the ability of rats to compensate for the stress of severe H. The purpose of the present study was to repeat these earlier studies using another CI, Ibuprofen (I), to determine if the response to NM is characteristic of all CI or unique to NM. Each of the 10 experiments utilized 2 pentobarbitalized Sprague-Dawley rats. One rat (Re) received a 25 mg/kg iv infusion of I prior to H, while the control (Rc) received a similar volume of vehicle. Both were simultaneously bled into calibrated burets to 60 and 30 mmHg MAP and held at 30 mmHg until decompensation to 20% blood uptake after which the total blood volume was restored. RESULTS: The dose of I used induced a mild hypotension from 128 ± 5 to 114 ± 6 mmHg ($P<.05$), and the max blood loss was less for I than control (22.6 ± 1.4 vs 27.7 ± 1.5 ml/kg $P<.02$) suggesting that I inhibits the ability of these rats to reduce their vascular capacity in response to H. However, when the max blood volume was corrected for the starting MAP the resulting .291 ± .02 and .289 ± .03 ml/kg/mmHg were not significantly different. These results using I are essentially the same as those obtained with NM.

Supported in part by American Heart Association, Oklahoma Affiliate, Inc.

59.5

EFFECTS OF SCIATIC NERVE STIMULATION ON PORCINE HEMODYNAMIC RESPONSE TO HEMORRHAGE. J.D. O'Benar J.P. Hannon, V. Gildengorin* and R.F. Bellamy. Letterman Army Institute of Research, Presidio of San Francisco, CA 94129.

Pigs (25±5 kg) anesthetized with chloralose and urethane were used to determine the effects of sciatic nerve stimulation (square-wave, 70V, 0.3mA, 10 Hz bursts) on the physiologic responses to rapid hemorrhage (28 ml/kg over 15 min). Compared to sham-operated controls (n=10), a majority (n=17) of the stimulated animals showed significant elevations in blood pressure and cardiac output. There were no effects of stimulation on right atrial, pulmonary artery or pulmonary capillary wedge pressure. Although plasma epinephrine and norepinephrine levels were greatly elevated by hemorrhage, there was too much variability to ascertain responses to stimulation. Sectioning the nerve proximal (but not distal) to the stimulating electrodes abolished all hemodynamic effects. A minority of animals (n=6) showed hypotensive responses to sciatic stimulation. These responses may have been due to a selective activation of a subpopulation of afferents. We conclude that hemorrhage accompanied by afferent, possibly nociceptive, stimulation results in an altered hemodynamic status than exists following blood loss alone.

59.6

CARDIAC SARCOLEMMAL MEMBRANE NA-Ca EXCHANGE IN ENDOTOXIN SHOCK. J.L. Parker, C.G. Carlton, R.S. Keller, H.R. Adams, and C.C. Hale. Dept. Veterinary Biomedical Sci. and Dalton Research Center, University of Missouri, Columbia, 65211

Intrinsic myocardial dysfunction in guinea pig experimental endotoxin shock has been previously established using in vitro cardiac preparations contracting independently of supportive or depressive influences present in vivo. These studies provided functional evidence of altered sarcolemmal (SL) Ca regulation of the heart in shock. In the current study, cardiac SL Na-Ca exchange was evaluated using purified SL membrane vesicles prepared from ventricular tissue of endotoxin-shocked (ES) and control guinea pigs. ES animals received purified E. coli endotoxin (4 mg/kg; IP) 16 hrs prior to sacrifice. Baseline Na-Ca exchange activity (measured by $^{45}Ca$ accumulation in vesicles) was similar in control and shock SL vesicles. Stimulation of Na-Ca exchange activity by chymotrypsin (Am. J. Phys. 243:C191-C195, 1982) resulted in a 2-4 fold increase in the initial rate of exchange activity in control SL vesicles but not shock SL vesicles. Endotoxin incubation in vitro with control SL vesicles had no effect on Na-Ca exchange activity over a wide range of endotoxin concentrations. Similarly, endotoxin perfusion in isolated heart preparations have failed to show the intrinsic myocardial dysfunction observed in hearts from ES guinea pigs (Am. J. Phys. 248:H818-H826, 1985). These results suggest that endotoxin shock indirectly perturbs cardiac Na-Ca exchange, which may then contribute to shock related myocardial dysfunction.

59.7

GLUCOSE DISAPPEARANCE IN DIABETIC RATS FOLLOWING GRAM-NEGATIVE INFECTION. JJ Spitzer, C Dobrescu* GJ Bagby and CH Lang. Dept. of Physiology, LSU Med. Ctr., New Orleans, LA 70112.

We examined the reported exacerbating effect of sepsis on glucose metabolism in diabetes. Diabetes was induced in rats by iv injection of 70 or 45 mg/kg streptozotocin (STZ). The higher dose of STZ produced severe diabetes ("overt", OD) characterized by fasting hyperglycemia and a left shift in the glucose tolerance curve (GTC); whereas, the lower dose produced a milder "latent" diabetes (LD) with fasting euglycemia and lesser alterations in GTC. After 4 wks, rats were catheterized and sepsis induced by ip injection of live E. coli; nondiabetic controls (ND) were injected with sterile saline. After 24 hrs of sepsis blood glucose was unchanged in ND and LD rats compared to nonseptic rats, but glucose fell from 15 to 8 mM in the septic OD group. Plasma insulin levels in the nonseptic OD were reduced 50% compared to ND and LD. Sepsis increased insulin in ND rats 66%, but not in the LD and OD rats. During the IV GTT glucose disappearance (K,%/min) was decreased in nonseptic diabetic rats (C=1.08±0.08, LD=0.69±0.05, OD=0.41±0.04). Sepsis increased K in ND rats (1.31±0.05), but had no effect in diabetic rats. After the glucose load, the peak increase in plasma insulin was greater (70%) in the septic ND rats than in nonseptic ND. Septic and nonseptic LD rats increased insulin to a similar extent; OD rats failed to increase plasma insulin. These results suggest that sepsis does not alter glucose disappearance in diabetic rats, while it enhances glucose uptake in control rats. (Supported by NIH GM 32371).

59.8

ENDOTOXIN INCREASES UPTAKE AND PHOSPHORYLATION OF 2-DEOXY-GLUCOSE BY SKELETAL MUSCLE OF CONSCIOUS RATS. K. Mészáros*, G.J. Bagby, C.H. Lang and J.J. Spitzer. Department of Physiology, LSU Medical Center, New Orleans, LA 70112

Administration of endotoxin (ET) is known to stimulate glucose utilization. Since skeletal muscle accounts for about one third of whole body glucose utilization at rest, this study was undertaken to estimate the effect of ET on glucose consumption by different muscle types, applying the 2-deoxyglucose (2-dG) tracer technique. Chronically catheterized, 24 h fasted rats received 100 ug/100 g E. coli ET or saline. Three hours later they were injected iv with radiolabeled 2-dG. Tissues were sampled 260 min post-ET and analyzed for radioactivity in 2-deoxyglucose-6-phosphate (2-dGP). ET increased the 2-dGP content in gastrocnemius, white and red portions of quadriceps femoris and abdominal muscles 1.5 to 2-fold, and in the diaphragm 4-fold. No such effect was noted in the brain. Glucose uptake by muscles was directly proportional to the uptake and phosphorylation of 2-dG, since the following criteria were met: a) plasma glucose concentration 3 h post-ET was not different from that in controls; b) in vivo ET administration did not affect the extent of discrimination against the analogue in glucose pathways (lumped constant), as determined in vitro; and c) retention of 2-dGP by tissues, as demonstrated by a sequential double-labeling technique, was unaltered after ET treatment. We conclude that the skeletal muscle mass contributes significantly to the increase in the rate of glucose disappearance after endotoxin administration. (Supported by NIH GM 32654.)

59.9

INCREASED GLUCOSE METABOLISM BY EPITROCHLEARIS MUSCLE REMOVED FROM ENDOTOXIN-TREATED RATS. GJ Bagby, CH Lang, ME Giaimo* and JJ Spitzer. Physiology, LSU Med. Ctr., New Orleans, LA 70112.

The rate of glucose disappearance is elevated in vivo after endotoxin (ET) indicating an enhanced rate of extrahepatic glucose uptake. Since ET results in redistribution of blood flow and release of a variety of mediators, it is important to also investigate ET-induced changes in carbohydrate metabolism under in vitro conditions. In this study glucose metabolism was assessed in epitrochlearis muscle taken from control and ET-treated rats. ET (1mg/100g BW) or saline was administered iv to rats and the epitrochlearis muscle removed 3 hrs later for in vitro incubation. Glycolysis, determined as $^3H_2O$ production from [2-$^3$H]-glucose, was increased 45% in muscles taken from ET-treated rats compared to control animals. Glycogen synthesis, assessed by the incorporation of [U-$^{14}$C]-glucose into glycogen, was similarly elevated. Glycolysis and glycogen synthesis were stimulated by insulin in a dose dependent manner; differences were still evident at the maximal effective insulin dose. However, muscles removed from ET-treated rats were more sensitive to insulin at submaximal doses of insulin. ET-induced changes in glucose metabolism were not reversed in the presence of indomethacin (10uM) indicating that prostaglandin production is not responsible for these changes. Thus, endotoxemia results in changes in glucose metabolism in skeletal muscle that are retained in vitro in the absence or presence of insulin. (Supported by NIH GM 32654).

59.10

IL-1 ALTERS GLUCOSE-INDUCED INSULIN LEVELS AND POTENTIATES GLUCOSE CLEARANCE RATES. N.A. Sacco*, M.R. Yelich and J.P. Filkins. Loyola Univ. Med. Center, Maywood, IL 60153

A glucoregulatory monokine such as interleukin-1 (IL-1) may contribute to glucose dyshomeostasis during gram-negative sepsis and endotoxicosis. The role of IL-1 as a mediator of hyperinsulinemia and hypoglycemia was therefore evaluated. Fed male Holtzman rats (380±10 g; n=4/grp) were anesthetized (sodium pentobarbital) and grouped into 5 IV treatment protocols: a) 1ml saline; b) 400mg/ml glucose; c) 400mg/ml glucose + 2500U rIL-1 (recombinant murine; Hoffmann-LaRoche); d) 400mg/ml glucose + 25U rIL-1 or; e) 2500U rIL-1. Plasma glucose (G), lactate (L) and immunoreactive insulin (IRI) levels were measured every 10 min. for 40 min. following treatment. Both doses of rIL-1 resulted in significantly lower half-times ($t_{½}$) of G clearance when compared to Group b ($t_{½}$ = c:22.0±4.0, d:26.4±6.0, b:38.3±4.5 min.;$p \leq .05$). The increase in G clearance rate induced by rIL-1 occurred in conjunction with biphasic hyperinsulinemia, compared to monophasic hyperinsulinemia in Group b. With G challenge alone, peak IRI (138.2± 10.7 uU/ml) occurred at 20 min. In G + rIL-1 treated groups, peak IRI occurred at 10 and 40 min. (c:115.2±7.4 uU/ml, d:90.4 ±1.5 uU/ml; and c:120.3±26.0 uU/ml, d:123±13.4 uU/ml). rIL-1 alone did not affect basal G levels. L levels remained normal in all groups. In conclusion, rIL-1 significantly potentiated G clearance and altered the pattern of hyperinsulinemia following G challenge. Therefore, IL-1 may be involved in mediating glucose dyshomeostasis during septic shock. (Supp. by HL31163).

59.11

CENTRAL AND PERIPHERAL SITES OF ACTION FOR ENDOTOXIN IN STIMULATING LIVER REGENERATION. Robert P. Cornell and David B. Schwartz*. Northeast Missouri State Univ. Kirksville, MO

A recent publication from this laboratory (Am. J. Physiol. 249:R551-R562, 1985) reported that intravenous bacterial endotoxin stimulates liver regeneration following partial (67%) hepatectomy of male Holtzman rats. $^3$H-Thymidine is injected at a dose of 10 µCi/100 g iv and the remaining right lateral lobe of the liver is removed 60 min later for evaluation of radionucleoside incorporation into hepatic DNA. While incorporation of $^3$H-thymidine peaked at 24 hr post-hepatectomy in untreated rats, the value at 18 hr post-hepex in saline-injected animals of 8±1.5 dpm/µg DNA (n=16) was enhanced to 105±13.4 dpm/µg (n=8) by administering endotoxin iv at a dose of 33 µg/100 g 24 hr prior to hepex. In order to determine the minimal amount of endotoxin capable of stimulating liver regeneration when administered 24 hr prior to hepex, $^3$H-thymidine incorporation at 18 hr post-hepex was found to be altered to 29±3.8 dpm/µg (n=12) by 3 µg/100 g of endotoxin intravenously and to 3±0.3 dpm/µg (n=11) by 3 ng/100 g of endotoxin intracerebroventricularly. However, when the two endotoxin doses were given simultaneously (3 µg/100 g iv and 3 ng/100 g icv), $^3$H-thymidine incorporation at 18 hr posthepex was enhanced to 93±14.2 dpm/µg (n=9) from 7±1.7 dpm/µg (n=12) in control animals. These findings suggest that endotoxin has both central and peripheral sites of action which are necessary for stimulating liver regeneration. (Supported by NSF DCB-8417355).



62.1

INCREASED $^{99m}$Tc-DTPA CLEARANCE FROM THE LUNG FOLLOWING EXPOSURE TO AEROSOLIZED PARAQUAT IN THE CONSCIOUS SHEEP. Robert A. Gunther, William J. Hornof,* Red S. Howard* and Paul Fisher*. Univ. of California, Davis, CA 95616

Enhanced clearance of $^{99m}$Tc-DTPA ($^{99m}$Tc-diethylenetriaminepentacetate) is associated with epithelial injury in the lung. The purpose of this study was to determine if short exposure to aerosolized paraquat would result in altered clearance of $^{99m}$Tc-DTPA in sheep. Four sheep were studied before and 24 hours after exposure to aerosolized paraquat. The aerosol was administered with sheep anesthetized and intubated for 15 minutes using an acorn nebulizer. Between 60-250 mg of paraquat was delivered to the lung. After 24 hours, $^{99m}$Tc-DTPA clearance was measured using a gamma camera and monitoring the sheep for 2-3 hours to determine the halftime ($t_{½}$) for removal of $^{99m}$Tc-DTPA from the lung. The time-clearance data were fitted to determine the exponential $t_{½}$ which, 24 hours after exposure to 150-250 mg paraquat, decreased to 27-57% of baseline. The baseline $t_{½}$ ranged from 118-440 minutes. Two animals were imaged again more than 48 hours post paraquat, and $t_{½}$ returned to baseline values. At the lowest dose (60 mg), no change was noted. In conclusion, aerosolized paraquat in the sheep reduced the $^{99m}$Tc-DTPA clearance significantly and these findings are suggestive of reversible pulmonary epithelial injury occurring at this dose of paraquat.
Supported by the American Lung Association/ATS.

62.2

EFFECTS OF LUNG VOLUME ON THE COMPARTMENTAL ANALYSIS OF ALVEOLAR SOLUTE CLEARANCE IN SHEEP. Barry T. Peterson, Harold L. James*, and Jerry W. McLarty*. Univ. of Texas Health Center at Tyler, Tyler, Texas 75710

The measurement of the lung clearance rate (k, %/min) of aerosolized $^{99m}$Tc-diethylenetriamine pentaacetate (DTPA) by nuclear imaging is sensitive to the background activity due to recirculation of the tracer. We developed a model that uses measured blood activities of DTPA to estimate the background activity in the blood and tissue measured by the gamma camera during a 2-hour study in 16 anesthetized sheep. The end expired pressure was 10 $cmH_2O$ for 8 sheep throughout the study (PEEP) and zero in 8 Control sheep. A compartmental analysis determined the minimum number of compartments (Comp) necessary to describe the data with a minimum error (Error). Seven additional sheep were ventilated with $^{99m}$Tc-labeled albumin (4 Control, 3 PEEP). The results (mean ± S.D.) were:

| | DTPA | | | ALBUMIN | |
|---|---|---|---|---|---|
| | k (Comp 1) | k (Comp 2) | Error | k (%/min) | Error |
| CONTROL | 0.4 ± 0.2 | | 0.8% | 0.02 ± 0.01 | 1.7% |
| PEEP | 0.4 ± 0.2 (56%) | 8 ± 4 (44%) | 1.2% | 0.02 ± 0.01 | 1.4% |

Two compartments were necessary only for DTPA in the sheep with PEEP. Lung inflation increased the clearance rate of half the DTPA and none of the albumin. Albumin may be better for discriminating lung injury from lung inflation.

62.3

PRECOCIOUS INDUCTION OF SURFACTANT PROTEIN BY 8-Br-cAMP DURING EMBRYONIC MOUSE LUNG DEVELOPMENT IN SERUMLESS, CHEMICALLY-DEFINED MEDIUM. Tina F. Jaskoll, Grace Don and Harold C. Slavkin*. Lab. Developmental Biology, University of Southern California, Los Angeles, CA 90089-0191.

The apoproteins of pulmonary surfactant are essential for normal surfactant function. During mouse lung organogenesis, surfactant protein is produced during 18-days gestation fetal lung development. We recently developed a serumless, chemically defined (BGjB + ascorbic acid) organ culture system permissive for de novo surfactant protein expression. To assess precocious surfactant protein expression in vitro, we compared dexamethasone (dex) with 8-brome-cAMP (8-Br-cAMP) on 12-days gestation embryonic B10.A mouse strain lung rudiments in serumless, chemically-defined medium. Surfactant protein expression was detected using anti-human surfactant IgG antibody (1:250 dilution) and dot-immunobinding assay. Dex supplemented cultures showed induction of protein by 6 days in vitro ($10^{-8}$M), whereas 8-Br-cAMP showed precocious induction by 3 days in vitro (either 50uM or 100uM), with significant increases by 6 days. This in vitro model is suitable for studies of cAMP-dependent protein kinase, calcium-dependent protein synthesis and protein phosphorylation during embryonic and fetal mouse lung organogenesis. These studies were supported by research grant HL28325, NIH, USPHS.

62.4

BIOPHYSICAL STUDIES OF A SURFACE ACTIVE MATERIAL (SAM) FROM RABBIT LUNGS. Kim Reilly*, Richard Mendelsohn* and Alan J. Mautone* (SPON: Emile M. Scarpelli). Dept. of Chemistry, Rutgers University, Newark, N.J. and Research Ctr., Schneider Children's Hospital-LIJMC, New Hyde Park, N.Y. 11042.

SAM with a chemical composition consistent with lung surfactant, and with the ability to lower surface tension to ⩽10 dynes/cm, has been isolated from rabbit pulmonary lavage. The thermotropic properties of SAM have been characterized with the techniques of Fourier Transform Infrared (FT-IR) spectroscopy and differential scanning calorimetry (DSC). FT-IR melting curves were constructed from the temperature-dependence of the lipid CH2 symmetric stretching vibrational frequencies near 2850 cm(-1). A broad gel-liquid crystal phase transition was observed in the range 20-35°C, with slight sample-to-sample variations in temperature. A similar temperature range was noted in DSC endotherms. Calcium ion (5-10 mM) increased the onset temperature of the lipid melting event, and induced an ordering of SAM and of its lipid extract at all temperatures studied. The effect on the lipids was suggestive of a Ca-induced phase separation caused by ion binding to phosphatidylglycerol and other acidic components. Interaction between Ca ion and the phosphate groups was demonstrated through Ca(2+)-induced shifts in the 1090 cm(-1) phosphate frequency. Removal of most of the protein component from the surfactant caused little effect on the thermotropic properties of the lipid fraction as observed by FT-IR.

62.5

TREATMENT OF CYSTIC FIBROSIS WITH LONG TERM PARENTERAL NUTRITION. Jeffrey Askanazi, Michael Rothkopf*, Stanley Rosenbaum,* and Elizabeth Ross,* Department of Anesthesiology, Columbia University, New York NY 10032 and Medical Service, Veterans Administration Medical Center, East Orange NJ 07019.

This paper reports on preliminary results using long term parenteral nutrition (including fat emulsions) for the treatment of cystic fibrosis. Three patients were placed on home parenteral nutrition for periods of 17 months, 3 months and 2 months. Parenteral nutrition was administered daily with a regimen of amino acids, dextrose and fat. Caloric intake was set to result in approximately 2 lbs/month weight gain and included 1000 kcal of fat emulsion daily (Intralipid, KabiVitrum, Inc, Alameda CA). Marked clinical improvement and exercise tolerance occurred in the patient who received parenteral nutrition for 17 months. Pulmonary function, which had previously deteriorated, stabilized and the patient reported that pulmonary secretions became thinner. The improvement exceeded that expected from the effects of improved nutrition alone. Moderate improvement occurred in the 2 patients studied for shorter periods. Long term parenteral nutrition seems to be a useful treatment modality in patients with cystic fibrosis. We postulate that the improvement was due to nutritional effects as well as a possible interaction between the fat emulsions and lung prostaglandins to reduce pulmonary inflammation. It should be emphasized that these findings are of a preliminary nature.

62.6

NICOTINE IS A SECRETAGOGUE OF PULMONARY ENDOCRINE CELL CALCITONIN. Ali R. Tabassian, Marie M. Cassidy, Richard H. Snider*and Kenneth L. Becker* Veterans Administration Med Center and George Washington University, Washington, DC 20422.

The respiratory tract of mammals, including man, contains endocrine cells which are part of the diffuse neuroendocrine cell system. These cells, commonly called pulmonary endocrine (PE) cells, secrete, among other hormones, the polypeptide calcitonin (CT). The PE cells appear to be sensitive to hypoxia, and it has been suggested that they function as chemoreceptors within the respiratory tract. Previously, we have shown that cigarette smoke inhalation causes release of CT from hamster lungs. This response was greater when high-nicotine cigarettes were used. In order to further study the role of nicotine in cigarette smoke-induced CT secretion, animals were injected with 1, 4 or 7 mg of nicotine/Kg body weight subcutaneously. There was a dose-dependent increase in serum CT and a decrease in lung tissue CT. With the highest nicotine dose, the response was submaximal. Nicotine also caused an increase in serum CT following thyroparathyroidectomy, ruling out the thyroid as the source of nicotine-induced CT secretion. Subcutaneous injection of an equimolar dose of the autonomic ganglionic blockers, hexamethonium and pentolinium, abolished the effect of nicotine, but atropine did not. These results indicate that nicotine, whether present in cigarette smoke or when injected, stimulates CT secretion from the lung through its effect on the autonomic ganglia.

62.7

NASOPHARYNGEAL AND LUNG REMOVAL OF OZONE DURING TIDAL BREATHING IN MAN. Timothy R. Gerrity, Richard A. Weaver*, Jon H. Berntsen*, John J. O'Neil. Clinical Research Branch, USEPA, Research Triangle Park, NC 27711; Department of Environmental Sciences and Engineering, School of Public Health, UNC; EMSI, Chapel Hill, NC 27514.

In a controlled environmental chamber, we measured the efficiency of ozone removal by the nasopharynx and lungs in 10 healthy nonsmoking young adult male volunteers by drawing air from the posterior pharynx through a French #8 polyethylene tube that was connected to a rapidly responding ozone analyzer. Tidal volume targets were established during spontaneous resting breathing. Measurements were made using a randomized split-plot design for each subject at three different ozone concentrations (0.1, 0.2, and 0.4 ppm), using three different modes of breathing (oronasal, nasal, and mouth) and two different respiration frequencies [12 and 24 breaths per minute (bpm)]. There were small but significant ($p<0.05$) effects of breathing mode on nasopharyngeal removal of ozone, with 48.1+/-1.07%, 41.3+/-1.06%, and 45.0+/-1.06% removed during oronasal, nasal, and mouth breathing respectively; and of frequency with 46.0+/-0.9% and 43.6+/-0.9% removed at 12 and 24 bpm respectively. There was a significant breathing frequency effect on total lung ozone removal with 89.2+/-0.4% removed at 12 bpm and 85.3+/-0.4% removed at 24 bpm. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.

62.8

COMPARISON OF THE EFFECT OF EPITHELIUM (EPI) REMOVAL ON REACTIVITY TO HISTAMINE (H) AND METHACHOLINE (MCh) OF GUINEA-PIG TRACHEALIS FROM NORMAL AND VITAMIN A-DEFICIENT ANIMALS. D. Raeburn*, D.W.P. Hay*, M.G. Mawhinney* and J.S. Fedan* (SPON: D.G. Frazer). DRDS, NIOSH and West Va. Univ. Med. Ctr., Morgantown, WV 26505, and Dept. of Pharmacol., Smith, Kline & French Laboratories., Philadelphia, PA 19101.

EPI removal increases the sensitivity of isolated airway smooth muscle to H and M which may involve the loss of modulatory factors from the EPI. Vitamin A deficiency results in a squamous metaplasia of the airway EPI. We have investigated whether the removal of transformed EPI from vitamin A-deficient animals produces similar results compared to normal diet controls. In tissues removed from normal diet animals EPI removal increased the sensitivity of GPT to H ($pD_2$s: +EPI: 6.38±0.11; -EPI: 6.74±0.09) and MCh ($pD_2$s: +EPI: 6.17±0.32; -EPI: 6.79± 0.13). In tissues from vitamin A-deficient animals EPI removal increased the sensitivity to H ($pD_2$s: +EPI: 5.34±0.13; -EPI: 5.77±0.06) but not to MCh ($pD_2$s: +EPI: 5.92±0.30; -EPI: 6.30±0.40). In addition to these alterations in the effect of EPI removal, the sensitivities of the tissues to H and MCh were reduced (see above) by ca. 10- and 2-fold, respectively. These results indicate that 1) the increased responsiveness to H and MCh in normal tissues after EPI removal may be mediated by more than one modulatory mechanism and 2) vitamin A deficiency reduces airway smooth muscle sensitivity.

62.9

BRONCHOCONSTRICTOR POTENTIAL OF INTRAVASCULAR C3a
J.W. Watson*, N.P. Stiller-Gerard* and J.K. Drazen. Department of Medicine, Beth Israel Hospital and Harvard Medical School, Boston, MA 02215.

The anaphylatoxin peptide C3a is generated during activation of serum complement and is a potent spasmogen for in vitro smooth muscle preparations. In vivo, the action of C3a is thought to be controlled by serum carboxypeptidase N (SCPN) which converts it to the inactive des arginine form. This anaphylatoxin, therefore, is not considered to contribute significantly to inflammatory reactions in vivo. We examined this hypothesis by determining the in vivo bronchoconstrictor potential of C3a, its modulation by SCPN and by pulmonary vascular leak. Guinea pigs were anesthetized, (50 mg/kg chloralose, 500 mg/kg urethane) tracheostomized and ventilated while pulmonary resistance (RL) and dynamic compliance (Cdyn) were monitored. Control animals recieved a single dose (6-600 ug/kg) of purified porcine C3a. A second group of animals was pretreated with 2-mercaptomethyl-3-guanidinoethyl-thiopropanoic acid, an inhibitor of SCPN (80 mg/kg i.v.) 20 min prior to C3a. A third group of animals was pretreated with i.v. histamine to induce vascular leak before C3a infusion. Histamine resulted in a significant increase in pulmonary vascular permeability as assessed by the ratio of 125I-labelled bovine serum albumin in the lung to that in the blood. In control animals the ED 200 RL for C3a was 110 ug/kg; the ED 50 Cdyn was 150 ug/kg. SCPN-INH pretreatment had no effect on the C3a response at doses less than 200 ug/kg; at 200 ug/kg the RL response was potentiated 4 fold over the control. Histamine pretreatment had a marked potentiating effect at all C3a doses, shifting the ED 200 RL by more than 10 fold. Our data indicate that SCPN does not influence C3a activity at low C3a concentrations. Further, C3a is capable of causing significant bronchoconstriction in the presence of enhanced vascular permeability as induced by histamine.

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62.10

TACHYKININS INHIBIT ENKEPHALINASE ACTIVITY FROM TRACHEAS AND LUNGS OF FERRETS.
D.B. Borson, B. Malfroy*, M. Gold*, J. Ramachandran*, and J.A. Nadel. Cardiovascular Research Institute, University of California, San Francisco, CA, 94143.

Previous studies (Fed. Proc. 43:626, 1986) demonstrated that enkephalinase inhibitors potentiated tachykinin-induced macromolecular secretion from ferret tracheas. To determine the distribution and activity of tracheal enkephalinase against tachykinins, we measured the degradation of $^3$H-Tyr, D-Ala$^2$,leucine-enkephalin. Ferrets were anesthetized with sodium pentobarbital (45 mg/kg, ip). The vagus (VN) and recurrent laryngeal (RLN) nerves, lungs (L), tracheal epithelium (E), muscle (M), and submucosa (S) were removed and each tissue was homogenized. Enkephalinase was found in each extract, with activities (in fmoles/min/mg protein) as follows: L, 1285±464; RLN, 653±174; VN, 921±325; S, 872±129; E, 925±290; M, 736±306 (n=5 each). Then we purified enkephalinase from 6 kidneys using published methods. Leucine-thiorphan inhibited activity in all cases ($K_I$=3-7 x $10^{-9}$M), whereas captopril, bestatin, aprotonin, and leupeptin (each drug, $10^{-5}$M) were without effects (n=3 each). Substance P and neurokinin A inhibited substrate cleavage with inhibition constants of between $10^{-6}$ and $10^{-4}$ M. These results indicate that tracheal and pulmonary enkephalinase interact with tachykinins, demonstrating its suitability for regulating tachykinin-induced airway responses.

Supported in part by NHLBI PPG HL-24136.

62.11

TRANSEPITHELIAL PROSTACYCLIN ($PGI_2$) GRADIENT IN ISOLATED CANINE TRACHEAL SEGMENTS (CTS).
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Recently cyclooxygenase products have been measured in airway lavage fluid to evaluate the role of prostaglandins (PG) in the regulation of airway caliber. To test the hypothesis that concentration differences for PG exist across airway epithelium we measured $PGI_2$ (the predominant PG produced by isolated CTS on the epithelial (E) and serosal (M) sides of isolated CTS. The posterior membranes of 9 CTS from 4 dogs (overdosed with pentobarbital) were mounted in physiological salt solution (37°C, gassed with 95% $O_2$, 5% $CO_2$) between modified Ussing chambers with one bath exposed to the E and the other to M. Segments were incubated for 2 hours with frequent exchanges of bath fluid. Aliquots of bath fluid were then withdrawn after 10 minute incubations and frozen for subsequent analysis. Samples were extracted using octadecylsilicyl silica cartridges and purified with reverse phase high pressure liquid chromatography (HPLC). Fractions with retention times similar to authentic 6-oxo-$PGF_{1\alpha}$ (degradation product of $PGI_2$), were measured by radioimmunoassay. Efficiency of extraction of HPLC averaged 91.2 ± 7.2%. 6-oxo-$PGF_{1\alpha}$ levels in a given bath were reproducible. However, 6-oxo-$PGF_{1\alpha}$ efflux was significantly higher on M than E (427 ± 125 pg.g$^{-1}$.min$^{-1}$ vs 206 ± 73; mean ± 1 SE; $p < 0.05$). These results demonstrate a substantial transepithelial 6-oxo-$PGF_{1\alpha}$ concentration gradient and suggest that $PGI_2$ in the airway lumen may not reflect the concentration of $PGI_2$ to which TSM is exposed. (Supported by the Medical Research Council of Canada).

62.12

KINETICS OF CANINE TRACHEAL CILIARY BEAT FREQUENCY AFTER AEROSOLIZED FENOTEROL
Lid B. Wong, Irving F. Miller, and Donovan B. Yeates. Departments of Bioengineering and Medicine, University of Illinois, and West Side Veterans Administration, Chicago, IL., 60612.

Beta-2 adrenergic agonists have been shown to stimulate ciliary beat frequency (CBF) in vitro however the time course of this potential stimulation in vivo has not been studied. After beagle dogs were sedated with acepromazine and anesthetized with Surital, CBF measurements were made on the ventral surface of the trachea using a correlation analysis laser light scattering system (Fed. Proc. 45(4): A3670). Eight dogs were studied twice. After baseline measurements of CBF, either aerosolized isotonic saline or $10^{-5}$ M fenoterol in isotonic saline was administered in a randomized blinded fashion and measurements of CBF made sequentially throughout the following 60 minutes. When fenoterol was administered, there was a 10 to 15 min latent period followed by stimulation of CBF which lasted for 30 to 40 min. with a peak effect at 20 to 40 min post inhalation. In these fenoterol studies CBF increased from a baseline of 6.8±2.4 beats/s to 24.9± 14.1 beats/s ($p<0.01$). In the placebo studies the CBF increased from a baseline of 7.2±2.5 beats/s to 8.6±2.9 beats/s ($p<0.05$) for the same time periods. The stimulation after fenoterol was significantly higher than after the placebo ($p<0.01$). Increased CBF after aerosolized fenoterol is one mechanism responsible for the observed increase in mucociliary transport following its administration (JAP 39(3): 487-495, 1975).

## CONTROL OF BREATHING

63.1

FIRING PATTERNS OF MEDULLARY RESPIRATORY NEURONS IN CHICKENS - EFFECTS OF $CO_2$ & STRETCH.
E. Keith Michal & Albert L. Kunz. The Ohio State University, Columbus, OH 43210

Scattered medullary neurons whose firing frequencies modulate with respiratory movements were recorded extracellularly in awake decorticate chickens. Neurons were classified by phase of maximal activity as inspiratory (I) or expiratory (E). Subclassifications of late, early, phase spanning, and plateau or augmenting were utilized to describe activity of different types. Observed $CO_2$ and stretch effects in some neurons were - Inhibition of I & E neurons by step decrease in $CO_2$ levels. Excitation of I neurons by step increases in $CO_2$. Steady state stretch (i.e. increased volume) resulted in decreased firing rates in I & E neurons. Step increases in volume (stretch) increased I neuron firing rate. Decreasing levels of steady state $CO_2$ resulted in increased firing frequency in respiratory neurons. (Supported in part by GHLBI Grant # HL23780).

63.2

ANALYSIS OF RESPIRATORY CHANGES ELICITED BY FASTIGIAL NUCLEUS (FN) STIMULATION IN PARALYZED, ANESTHETIZED CATS.
L. O. Lutherer and J. L. Williams. Depts. Physiol and Int. Med., Texas Tech Univ. Health Sciences Center, Lubbock, Tx. 79430

We reported (Am. J. Physiol. 250: R418-R426, 86) that 30-s stimulus trains to rostral FN alter ventilation in spontaneously breathing cats. At all sites at lower Hz, frequency (f) was increased and inspiratory duration ($T_I$) shortened. Changes in tidal volume were variable. At half the sites, stimulation at higher Hz induced an initial transient apnea. In the present study, phrenic nerve activity was recorded in anesthetized, paralyzed, artificially ventilated cats. Neural correlates of respiratory activity including f and $T_I$ showed responses to FN stimulation very similar to those observed in the spontaneously breathing cat. At 200 Hz, however, all sites displayed an initial apnea. This was reversed or markedly attenuated when the $FICO_2$ was increased to 5%. Furthermore, tidal neural activity showed a significant increase, presumably reflecting the minimized reflex inhibition under fixed ventilation. The minute neural activity remained increased for 3-5 min after stimulation, with a subsequent prolonged inhibition. These results indicate that the respiratory changes induced by FN stimulation 1) are not due to somatic activation, 2) involve an influence on both central pattern generator and afterdischarge circuits, and 3) are interrelated with chemoreceptor input. (Supported by AHA 831235, Tarbox Institute, NIH HL 07289.)

63.3

DETECTION OF ENTRAINMENT (ENT) OF VENTILATION TO THE WALKING CYCLE IN MAN. A.R. Hill*, J.M. Adams, B.E. Parker*, D.F. Rochester. Univ. of Virginia Med. Ctr., Charlottesville, Va. 22908 and SUNY-Health Sci.Ctr., Brooklyn, N.Y. 11203.

We describe a new breath-by-breath analysis to test for ENT of breathing and walking cycles. Subjects (38 normal, 5 with lung disease) walked comfortably on a treadmill, breathing through a pneumotachygraph. We measured the time intervals between the beginning of inspiration (or expiration) and the right heel strike for all breaths during 3 minute runs. Criteria for ENT were that these intervals display fixed coupling to within $\pm$ 0.10 s for at least 3 consecutive breaths; this also ensures that stride frequency: breathing frequency ($f_s/f_b$) is a whole integer. The mean standard deviation ($\overline{SD}$) of coupling intervals for entrained breaths was 0.068 $\pm$ .017 s vs 0.313 $\pm$ .081 s for nonentrained breaths. ENT averaged 47 $\pm$ 25% of breaths and exceeded 40% in 27 subjects. The commonest coupling ratio ($f_s/f_b$) was 2:1, averaging 53% of entrained breaths. In separate runs where 10 subjects deliberately attempted to maintain ENT, ENT averaged 90 $\pm$ 12%, with coupling interval $\overline{SD}$ of 0.063 $\pm$ .020 s. We conclude that spontaneous ENT of breathing to walking is frequent but sporadic, with specific coupling patterns typically lasting only a few breaths at a time. The advantage of the breath-by-breath method is its ability to detect ENT even in short runs, and even when the ENT pattern (coupling ratio or interval) changes between ENT episodes.

63.4

CHARACTERIZATION OF CRICOTHYROID (CT) MOTOR UNIT ACTIVITY IN THE DOG. G. Sant'Ambrogio, F.B. Sant'Ambrogio, O.P. Mathew and G.E. Woodson*. Univ. Texas Medical Branch, Galveston, TX 77550 and Baylor College of Medicine, Houston, TX 77030.

The CT muscle can be activated either in inspiration or expiration or both. Are there specialized motor units for inspiration and expiration? We have recorded from single units in the external branch of the superior laryngeal nerve while monitoring the contralateral CT EMG in 9 anesthetized spontaneously breathing dogs. Motor unit action potentials, CT EMG, esophageal and upper airway pressures were recorded during tracheotomy and upper airway breathing, tracheal and upper airway occlusions. Motor unit discharge reflected the whole muscle activity: 47 motor units were recruited during inspiration and expiration, 13 discharged only in inspiration when the level of CT activity was low or absent. The level of CT activity at which a unit was recruited, as determined for 22, was equal in inspiration and expiration in 10, lower for inspiration in 5 and for expiration in 7. All the CT units tested were stimulated more by upper airway than tracheal occlusion at end expiration. Most of the units (15/20) tested were unaffected by peak inspiratory occlusions above or below the larynx, 4 were stimulated equally by both and 1 was activated only when the larynx was included. These results suggest that there are no specialized units for inspiration and expiration and that negative pressure in the larynx is a potent stimulus for CT activation.
Supported by NIH Grants HL-20122 and HL-01156.

63.5

CHANGES IN WORK OF BREATHING AND RELATED VENTILATORY PARAMETERS IMPOSED BY PRESSURE-DEMAND RESPIRATOR WEAR. J.R. Wilson*, P.B. Raven, D. Ostransky*, R.O. Garmon*& S.A. Zinkgraf*. Depts of Physio & Med, Tex Coll of Osteo Med, Fort Worth, Tx 76107 & Southwest Tex State Coll, San Marcos, Texas.

The present investigation was undertaken to evaluate the changes in total work of breathing ($WB_{TOT}$) and other ventilatory parameters imposed by a full face-piece, pressure-demand respirator during progressive exercise to maximal work. 38 healthy subjects (ages 20 to 51 years) underwent a treadmill ramp test to maximal oxygen uptake ($\dot{V}O_{2max}$). Respirator wear (R) decreased performance time (5%) from control (C), $p<0.05$, yet resulted in a higher $\dot{V}O_2$ ($p<0.01$). Changes in related ventilatory parameters at $\dot{V}O_{2max}$ are summarized below.

| | $\dot{V}_E$ (l/min) | $\dot{V}_T$ (l) | f (br/min) | $dv/dt_i$ (l/min) | $dv/dt_e$ (l/min) | $WB_{TOT}$ (J/min) |
|---|---|---|---|---|---|---|
| C | 120 | 2.61 | 42 | 281 | 324 | 258 |
| R | 119 | 2.85 | 38 | 268 | 289 | 271 |
| P | <.77 | <.001 | <.001 | <.063 | <.001 | <.434 |

Expired work of breathing was increased ($p<0.01$) and was related to a more significant increase in expired pressure, as expired flow was significantly decreased. However, there were no differences in $WB_{TOT}$ ($p>0.05$). We conclude that the increased $\dot{V}O_2$ at maximum work reflects the metabolic adjustments necessary to overcome the increased work of breathing during expiration. However, changes in effort sensing of breathing were related to the increased expiratory pressures and produced an alteration in the perception of work.
(Supported in part by NIH Grant #OHO1617).

63.6

EFFECTS OF CONSTRAINING VENTILATION ON THE SENSATION OF DYSPNEA DURING INCREASING CHEMICAL DRIVE. T. Chonan*, M.B. Mulholland*, N.S. Cherniack and M.D. Altose. Case Western Reserve Univ., Cleveland, OH 44109

The influence of thoracic displacement on the sensation of dyspnea is uncertain. This study examined the effects of limiting thoracic displacement, by constraining ventilation, on the intensity of dyspnea (D). During progressive hypercapnia produced by rebreathing, 10 normal subjects scored D on a visual analogue scale. Rebreathing was free (FR) in one trial, but was voluntarily constrained (CR) to the baseline tidal volume and frequency in another. There was a power function relationship between changes in $P_{ET}CO_2$ and D. At a given $PCO_2$, CR resulted in an increase in D. The absolute difference in D between the FR and CR trials increased with increasing $PCO_2$ but the fractional difference remained constant; the exponents of the power function relationships were the same in FR (2.14) and CR (2.23). The increase in the D at $PCO_2$ 50 mmHg during CR correlated significantly with the increase in tidal volume above baseline at the same $PCO_2$ in the FR trial ($r=0.76$). These results indicate that constraining ventilation below that demanded by the level of respiratory chemical drive accentuates dyspnea. This may be due to a loss of inhibitory feedback from mechanoreceptors acting either on brain stem or cortical centers. Supported by NIH grant HL 25830.

63.7

TECHNIQUE FOR SIMULATING CHANGES IN AIRWAY RESISTANCE AND CHEST WALL COMPLIANCE (INDEPENDENT OF CO2 REGULATION) IN THE AWAKE, UNIDIRECTIONALLY-VENTILATED CHICKEN D.R.Kariusᵃ and A.L.Kunz. Dept. of Physiology; Ohio State Univ., Columbus O.

Because bird lungs are tubular gas exchangers and do not expand during breathing, the pressure-volume curve of the thoracoabdominal air sac system shows no hysteresis. Therefore the causal relationship between respiratory effort (as inferred from Pa(t), the time varying active pressure component of air sac pressure and volume, V(t)), can be modeled as a first order bellows system with two parameters, R and C: $R\,dV/dt + V(t)/C = -Pa(t)$. We have previously reported (Fed. Proc. 42(4):1128, 1983) a servotechnique which forces V(t) to track a reference pattern independent of the animal's breathing efforts. By using a function of Pa(t) as the reference for forcing V(t), a computer algorithm is substituted for the respiratory bellows system. By using the above equation for this algorithm, Pa(t) is again in control of V(t) through a first order system with two parameters, "R" and "C". "R" and "C" are functionally analogous to R and C. Although changing the values of "R" and "C" does not change the physical parameters, it changes the correlation between the patterns of the motor output and sensory feedback as if R and C had been changed. "R" and "C" are easily manipulated over ranges of $+\infty$ to $-\infty$. Measured forces applied to a mechanical model of the chicken produce the predicted changes in V(t) as "R" and "C" are systematically varied. (Supported by Central Ohio Heart Chapter)

63.8

ROLE OF EPIGLOTTIS ON THE AFFERENT ACTIVITY OF THE SUPERIOR LARYNGEAL NERVE (SLN) IN THE RABBIT. H. Tsubone*, O.P. Mathew, G. Sant'Ambrogio. University of Texas Medical Branch, Galveston, TX 77550.

Differences in distribution and function of laryngeal receptors have been previously reported in rabbits as compared to cats and dogs. We studied the response of laryngeal afferents to transmural pressure (Ptm, -5 to +5 $cmH_2O$) and their respiratory modulation in seven anesthetized, spontaneously breathing rabbits. Laryngeal afferent activity was predominantly tonic during tracheostomy breathing and was increased by positive pressure and decreased by negative pressure accounting for expiratory modulation during upper airway breathing and occlusion. Restriction of epiglottal movement (n=6) in which an oral cannula was deeply positioned within larynx reduced (n=5) or abolished (n=1) the response to Ptm. Surgical removal of epiglottis (n=7) markedly reduced the tonic activity to 16.5% of control disclosing an inspiratory modulation, and in 4 of 6 rabbits reduced or abolished the responses to pressure changes. We conclude that 1) most of the afferent activity in the SLN originates from the epiglottis in rabbits and mediates the response to Ptm changes in the upper airway; 2) although the reflex responses to pressure changes in the larynx are similar in rabbits, cats and dogs, the pattern of activation of SLN afferents differs suggesting a different central processing of the afferent information.
Supported by NIH grants: HL20122 and HL01156

63.9

EFFECTS OF ARTERIAL $CO_2$ ON INTRAPULMONARY STRETCH RECEPTOR ACTIVITY DURING STATIC LUNG INFLATIONS. G.S. Mitchell and E.H. Vidruk. Univ. of Wisconsin, Madison, WI 53706.

To determine if $CO_2$ induced reflex bronchoconstriction alters the relationship between intrapulmonary stretch receptor (PSR) activity and static airway pressure (Paw), the effects of increased $PaCO_2$ on the relationship between PSR discharge frequency and Paw were determined in 15 dogs. PSR activity (n=38) was recorded in fine strands dissected from an otherwise intact vagus nerve while monitoring the integrated phrenic neurogram. Paw and gas compositions in the airways and arterial blood were controlled independently; Paw was varied between 2 and 14 cm $H_2O$ at levels of $PaCO_2$ between 35 and 85 mmHg while airway $CO_2$ was held constant. The response to Paw was variable among PSR but consistent in a given unit; however, there was no consistent effect of $PaCO_2$ on this relationship. Selected PSR (n=15) were averaged to yield a population response; the selection criteria were: 1) phrenic activity responded briskly to Paw; and 2) measurements were made at three levels of $PaCO_2$. Average PSR discharge increased linearly with Paw but was unaffected by $PaCO_2$. Phrenic burst frequency decreased as Paw increased, and hypercapnia attenuated the slope of this relationship. These results indicate that $PaCO_2$ effects on the PSR vs. Paw relationship cannot account for attenuation of the relationship between phrenic frequency and Paw in hypercapnia. The latter effect probably arises from mechanisms in the central nervous system. (Supported by N.I.H. grants HL-29607 and HL-01494).

63.10

**Avian Carotid Chemoreceptor Response to Oscillating Arterial pH and $PCO_2$.** S.C. Hempleman, M.G. Rietow* and F.L. Powell. Dept. of Medicine, UCSD, La Jolla, CA 92093.

**Single unit and several unit neural recordings were made from vagal filaments in 7 anesthetized, unidirectionally ventilated ducks. Inspired $CO_2$ was oscillated with a piezoelectric crystal gas valve causing 6 cycles/min of $F_ICO_2$ (ca. 0 to 6%) and $F_IO_2$ (ca. 9.7 to 10.3%, secondary to $CO_2$ addition). Receptor discharge, arterial pH (indwelling electrode), and inspired $CO_2$ were recorded by computer and each ensemble averaged over 5 to 40 stimulus cycles (typically 800 to 2048 action potentials). $F_ICO_2$ oscillations produced pHa oscillations of the same frequency, amplitude .05 to .08 units, lagging 2.5 to 3.5 seconds. Of 13 receptor filaments studied, 6 followed the $CO_2$/pHa oscillations with greater than 60% average cyclic change in discharge frequency. Maximum discharge occurred during the acid-going pH phase. Units displaying minimal static $CO_2$ sensitivity did not respond to $CO_2$ oscillation. $F_IO_2$ cycling was small enough that receptor static $O_2$ sensitivities predicted minor $O_2$-linked cyclic variations in discharge.**

**These results suggest that a portion of the avian carotid chemoreceptor population can provide feed-forward control information about slow respiratory linked pHa oscillations. (Supported by NIH HL-33379).**

63.11

RESPIRATION DURING SLEEP IN INFANTS AND YOUNG CHILDREN. Cl. Gaultier*, JP. Praud, E. Canet, AM. D'Allest. Lab. Physiol. Hosp. Béclère. 92141 Clamart - France.

Previous studies have shown that abnormalities in respiration during sleep are frequent in the neonatal period and the first months of life while they are rare in childhood, no study has concerned the intermediate period of growth. We wondered whether abnormalities persisted during infancy and early childhood. Eleven healthy subjects (7-26 mo) were tested during natural afternoon naps. Sleep stages (neurophysiological criteria), airflow (thermistors), $PO_2$ and $PCO_2$ (transcutaneous electrodes), thoracic and abdominal motion (magnetometers) were monitored. Total sleep time (TST) was equal to 138 min (107-186) including 15% (6-25) of REM sleep. Apneas longer than 5s were counted. Results are in table ; where apnea time (AT) was expressed as % of TST and NREM and REM sleep time(T), $\Delta PO_2$ and $\Delta PCO_2$ (mmHg) were maximal changes.

| | AT % TST | AT % REM T | AT % NREM T | $\Delta PO_2$ | $\Delta PCO_2$ |
|---|---|---|---|---|---|
| mean | 1.2 | 1.6 | 0.9 | 12.5 | 7 |
| range | 0.3 - 2 | 0.2 - 4 | 0.2 - 2 | 7 - 16 | 5 - 10 |

In contrast to the neonatal period 1) apneas were essentially central and no more frequent in REM than in NREM sleep 2) decreases in $PO_2$ occurred after apnea and not during rib cage distortion. Increase in $PCO_2$ occurred during stage 3-4 NREM sleep. We conclude that, despite improvement of sleep respiratory adaptation, infants and young children still have persistent abnormalities in respiration during sleep (Supported by Fac. Med. Paris XI, CNRS UA 1159).

63.12

APNEA IN PRETERM LAMBS: RECOVERY WHEN BREATHING AIR OR OXYGEN. A. A. Hutchison*, L. Reyes*, J.R. Mercer*, S.L. Evans*. (SPON: R.M. Abrams) Department of Pediatrics, University of Florida, Gainesville, FL 32610.

Eight unanesthetized preterm lambs, breathing spontaneously via an endotracheal tube placed into a tracheostomy, were studied during recovery from apnea. Apnea was induced by the instillation of 5 milliliters of distilled water onto the larynx. After a baseline 30 seconds (s), the standard apnea stimulus was given over 30s. The lambs then breathed air or oxygen during a 2 minute (m) recovery period, which started with a 15s period of artificial ventilation. At 2m the degree of recovery was less in the oxygen breathing group: minute ventilation ($V_I$) 381+/-27 air, 270+/-18, oxygen $p>0.01$; pH 7.38+/-0.005 air, 7.34+/-0.008 oxygen $p<0.01$; arterial carbon dioxide tension ($PaCO_2$) 45.0+/-1.3 air, 49+/-1.3 oxygen $p<0.01$; base excess 2.1+/-0.5 air, 1.1+/-0.5 oxygen $p<0.01$. By 2m a return to baseline values of $V_I$, pH and $PaCO_2$ was noted only in the air breathing group, where arterial oxygen tension also returned to normal. The heart rates at 2m were not different and, in both groups, were less than their baseline values. Following severe apnea, resuscitation with 100% oxygen can impair respiratory recovery. (Supported by DSR grant, University of Florida)

63.13

BREATHING ON A VALVELESS CIRCUIT. M.H. Wagner*, M. Jaeger, S.E. Chesrown*, University of Florida, Gainesville, FL 32610

This study evaluated the ventilatory responses of healthy, awake subjects while connected to a valveless (Bain) breathing circuit widely used during anesthesia. Rebreathing occurs with this system when the fresh gas flow (FGF) rate is less than the subjects' peak inspiratory flow. Minute ventilation ($\dot{V}_E$) and end tidal carbon dioxide ($ETCO_2$) were monitored in 10 healthy volunteers (5 men, 5 women) for 10 minutes in each of 4 conditions. Conditions were: 1) 40% $O_2$/60% $N_2$ through an open circuit with one-way valves, 2) 95% $O_2$/5% $CO_2$ through an open circuit with one-way valves, 3) 40% $O_2$/60% $N_2$ on the valveless circuit with FGF of 8 L/min, 4) 40% $O_2$/60% $N_2$ on the valveless circuit with FGF 4 L/min. At the end of condition 3, subjects were asked to maximally ventilate for 1 minute. Data from conditions 1 and 2 defined the subjects' $CO_2$ responsiveness. Results from conditions 3 and 4 fell near this response line. Subjects' $ETCO_2$ on the valveless circuit with FGF of 8 L/min was 4.0 torr higher than $ETCO_2$ obtained during baseline measurements on the valved circuit (paired t-test $p < .05$). However, the observed increase in $ETCO_2$ would be clinically insignificant. Maximum voluntary ventilation while on the valveless system resulted in only a 3.7 + 1.6 torr decrease in $ETCO_2$. In summary, $ETCO_2$ remains within an acceptable range at FGF of 8 L/min, although rebreathing occurs with the valveless circuit. Moreover, $ETCO_2$ is almost independent of $\dot{V}_E$. [Supported in part by the Cystic Fibrosis Foundation and Pediatric Pulmonary Center Grant MCJ2013]

63.14

ESTIMATION OF VENTILATORY GAIN FROM SPONTANEOUS BREATHING PATTERNS. M.C.K. Khoo*, V.Z. Marmarelis* and C. Vivo*, Univ. of Southern Calif., Los Angeles, CA 90089. (Spon: H. K. Chang)

Spontaneous ventilation (x), measured by inductive plethysmograph, and end-tidal $P_{CO2}$ (y) were monitored in normal volunteers over continuous periods of up to 1 hour. Correlation and spectral analyses of these data showed narrow-band oscillations superimposed on a broad-band background, suggesting that all extraneous influences may be lumped into a white noise input perturbing the respiratory control system. With this assumption, the steady state response to $CO_2$ (H) may be deduced from:

$$H = \{\sum_{n=d}^{N+d} \phi_{yx}(n)\}/\{\sum_{n=0}^{N} \phi_{yy}(n)\}$$

where N represents maximum lag (in breaths), D is a delay of 2-4 breaths, $\phi_{yy}$ is the autocorrelation of y, and $\phi_{yx}(n)$ is the crosscorrelation of y(i) with x(i+n), where for given i. We have performed extensive tests of this procedure on data generated by a respiratory control model perturbed by white noise. Estimated values of H correlated linearly with total (=central+peripheral) gain of the model with a slope of 1.09 (SE=.23). This method of estimating ventilatory gain from spontaneous breathing data may be particularly useful in situations (e.g., sleep studies) where $CO_2$ inhalation is undesirable. (Supported by the Whitaker Foundation).

63.15

DIAPHRAGMATIC VASODILATION FOLLOWING STIMULATION OF PULMONARY C-FIBERS WITH CAPSAICIN. J. Richard Coast, Regina M. Romeo*, Sharon S. Cassidy. Dept. Int. Medicine, UTHSCD, Dallas, TX.

Stimulation of pulmonary C-fibers with capsaicin (caps) is known to have profound effects on the cardiovascular and respiratory systems. It has also been shown to cause decreased vascular resistance in some skeletal muscles and in cardiac muscle. The purpose of these experiments was to determine if pulmonary C-fiber stimulation would cause vasodilation in the diaphragm as well. In eight dogs, the non-working left hemidiaphragm was perfused at a constant flow rate through a catheter in the left phrenic artery. Perfusion was from an extracorporeal reservoir, and pressure was measured from a side port to the catheter. Injection of caps (5-20 μg/kg) into the right ventricle (RV) caused a significant 16% decrease in phrenic perfusion pressure, along with a 35% decrease in systemic arterial pressure and a 21% drop in heart rate. Left ventricular (LV) injection of equal doses of caps produced no significant change in systemic arterial pressure, and only a 7 and 10% drop in phrenic perfusion pressure and heart rate respectively ($p<.05$). Vagotomy abolished the effects of both RV and LV injection of caps. Sympathetic ganglion blockade with hexamethonium bromide (2 mg/kg) also abolished the effects of caps injection. These experiments have shown that stimulation of pulmonary C-fibers with caps causes a vagally mediated reflex vasodilation in the diaphragm, the efferent limb of which is sympathetic in origin.

63.16

LONG TERM EFFECTS OF NEONATAL HYPOXIA IN THE NEWBORN RAT. Shuichi Okubo* and Jacopo P. Mortola. Department of Physiology and Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada H3A 2B4

In a previous study we have observed that newborn rats maintained in 10% $O_2$ for the first week after birth decreased body growth, had lower oxygen consumption ($\dot{V}O_2$) and higher minute ventilation ($\dot{V}_E$) than control rats growing in air. The lungs of the hypoxic rats were also bigger and heavier, relatively to their body size, than controls, with larger alveoli. We asked to which extent these morphological and functional changes would persist after termination of the hypoxic exposure. Newborn rats were kept in 10% $O_2$ during the first week of life, then returned to air breathing, and measurements were performed weekly. Body weight (BW) increased very little during hypoxia, but after return to air body growth was more than in control rats, and eventually BW reached the control value at 2 months of age. Both $\dot{V}O_2/BW$ (measured manometrically) and $\dot{V}_E/BW$ (measured by flow plethysmography or by the barometric method) were above control, probably reflecting the higher oxygen demands of rapidly growing animals. However $\dot{V}_E/BW$ remained increased even at 2 months, when both BW and $\dot{V}O_2/BW$ were as in controls. Hematocrit and heart weight/BW, elevated in hypoxia, returned to control within one week, while dry lung weight/BW remained above the control values as much as during the hypoxic exposure. These results suggest that early postnatal hypoxia in the rat determines changes in lung structure and, possibly, in the control of ventilation, which seem to persist until adulthood.

(Supported by the Medical Research Council of Canada)

## COMPARATIVE PHYSIOLOGY: RESPIRATION, CIRCULATION OSMOREGULATION, AND LOCOMOTOR ADAPTATIONS

64.1

RELATIONSHIPS BETWEEN VAGAL EFFERENT ACTIVITY AND PRESSURE IN THE AIR BREATHING ORGAN OF GAR. S. Qassim Azizi* and Neal J. Smatresk. Univ. of Texas at Arlington, Arlington, TX 76019

It has been suggested that trabecular smooth muscle tone in the lungs of some air breathing fish may be under vagal efferent control, and that efferent activity may in turn be reflexively modulated by pulmonary mechanoreceptor activity. To test this hypothesis whole nerve activity was recorded from the cut left pulmonary branch of the ramus intestinalis of the vagus along with lung pressure in anesthetized spontaneously ventilating gar (Lepisosteus oculatus and L. osseus). Air breathing attempts were correlated to changes in lung pressure and efferent activity, although spontaneous changes not associated with air breathing were observed in all gar. Spontaneous declines in lung pressure were correlated to decreased activity, while increased pressure was correlated to increased activity. Sudden inflation of the lung to maximum volume generally decreased efferent activity, while rapid lung deflation produced a burst of activity followed by an increase in activity over control levels. Bilateral section of the vagus abolished the correlation between lung pressure and efferent activity, as well as the reflex responses to lung inflation and deflation. Thus, pulmonary smooth muscle tone is under vagal efferent control in gar and pulmonary mechanoreceptors contribute to the control of efferent activity via vagovagal reflex pathways.

(Supported by NSF Grant PCM 8317914)

64.2

THE RELATIONSHIP BETWEEN ARTERIAL $PCO_2$ AND BICARBONATE ($HCO_3^-$) IN CHRONIC METABOLIC ALKALOSIS IN THE YUCATAN MINIATURE PIG. J.M. Terris. Dept. of Physiol., Uniformed Services Univ., Bethesda, MD 20814-4799.

Adult Yucatan miniature boars (85±2 Kg at the time of mineralocorticoid administration) were fed once daily a pre-measured quantity of a commercially available pig chow meal supplemented with NaCl to give approximately 4.5 mEq Na/Kg body wt. Water was available ad lib. Blood samples were obtained from indwelling arterial catheters. After 1-2 wks of stable baseline measurements pigs were implanted subcutaneously (Thiamylal anesthesia) with deoxycorticosterone-acetate (DOCA, 100 mg/Kg, N=9)- or aldosterone (Aldo 2.7 mg/Kg, N=8)-impregnated silicone rubber. Serum $HCO_3^-$ levels were calculated from measured whole blood pH and $PaCO_2$ using the Henderson-Hasselbalch equation. Alkalosis was evident 4-6 days post-implantation with DOCA or Aldo and was significantly different from pre-implantation pH by the end of the first week. A sig. correlation was found between $PaCO_2$ and $HCO_3^-$ (DOCA r=0.80, 104 observations; Aldo r=0.88, 93 observations) during the period of metabolic alkalosis from 5-21 days postimplantation when the observations were terminated. The regression equation relating $PaCO_2$ and $HCO_3^-$ for the combined data is 0.91 ($HCO_3^-$) + 11.5 (r=0.84), comparable to relationships found in the human, but not dog and rat, with metabolic alkalosis of several etiologies. Computation of predicted $PaCO_2$ from reported cases of metabolic alkalosis in humans without respiratory compromise revealed no overall significant difference from measured $PaCO_2$.

64.3

PULMONARY VASCULAR RESPONSE AND LUNG UPTAKE OF LIPOSOMES IN 7 ANIMAL SPECIES. K Miyamoto*, E Schultz* and NC Staub. Cardiovasc Res Inst & Dept Physiol, Univ Calif, San Francisco, CA.

We found that tiny quantities of liposomes injected i.v. caused large transient increases in pulmonary arterial pressure (Ppa) in sheep by a mechanism involving arachidonate metabolites (FED PROC 45:1159, 1986). Dogs did not respond. We hypothesized that the response correlated with the intracapillary population of macrophages in the lungs of ruminants (AJP 250:R728, 1986). We compared the change in Ppa with the organ distribution of $^{111}$In-labeled liposomes in 7 pentobarbital-anesthetized species. We made dose-response curves by injecting .2 or 5.5 μmol/kg total lipid intravenously over 1 min. Two hours after the last dose, we removed the lungs and other organs and measured their radioactivity. The data are summarized in the table (mean ± S.D.).

| Species | Δ Ppa(cmH2O) | Lung $^{111}$In (% injected) |
|---|---|---|
| sheep, goat, pig | 50 | 50-75 |
| ox, rabbit | 15 | 47(ox), 1(rabbit) |
| dog, rat | 0 | 1 |

In 5 species there is an excellent correlation between pulmonary vasoactivity and lung liposome retention. But ox (high retention) and rabbit (low retention) did not correlate well. The relationship between the intracapillary macrophages and pulmonary vascular reactivity is imperfect and is not limited to ruminants. [Supported in part by HL25816 (Program Project)].

64.4

WATER EXCHANGE OF TRIONYX TRIUNGUIS EGGS DURING INCUBATION. A. Leshem*, R.A. Ackerman, A. Ar*, R. Dmi'el*. Depts. Zoology, Tel Aviv University, Tel Aviv, Israel and Iowa State University, Ames, Iowa 50011.

The eggs of the Nile soft-shelled turtle, Trionyx triunguis have hard, calcareous shells and are buried 20-40 cm beneath the soil surface in clutches of 40 ± 5 eggs. The eggs in four natural nests were monitored in Israel. Eggs of two additional nests were removed for artificial incubation. Egg mass was measured at the beginning and end of incubation. Hatchling mass was measured. Soil water content and soil and nest temperatures were measured around and in the nests. Soil water content was related to water potential by measurement. Eggs in the laboratory were incubated at 30 ± 0.5°C and in one of four estimated water potentials (-16,000, -12,000, -3,500, -40 kpa). Soil water potential near natural nests was about -100 kpa at 40 cm deep and -25,000 kpa at 20 cm. Mean nest temperature increased from 26°C to 31°C during the nesting season. Eggs at the bottom of the nest lost 3.0 ± 4.5% of initial egg mass compared to 8.4 ± 8.8% at the top of the clutch. Hatchling mass ($\bar{x}$ = 12.1 ± 0.6 g) was not correlated with egg mass loss in the natural nests but was correlated with egg mass loss in the laboratory. Eggs at -16,000 kpa lost 43 ± 16.8% of initial mass and produced hatchlings weighing 8.8 ± 0.5 g. Eggs at -40 kpa gained 3 ± 3.5% and produced hatchlings weighing 11.5 ± 0.7 g. We conclude that eggs buried in a clutch lose less water than eggs incubated individually. Supported by BSF 84-00357.

64.5

EFFECT OF HYPOBARIC AND ISOBARIC HYPOXIA ON VENTILATION AND ARTERIAL BLOOD-GASES IN DUCKS. Frank L. Powell, Hashim Shams* and Steven C. Hempleman. Dept. of Med., Univ. of California, San Diego, La Jolla, CA 92093.

We tested the hypothesis that $PaO_2$ would be greater in hypobaric hypoxia than at a comparable level of isobaric hypoxia because of differences in gas phase diffusivity. Ventilation was measured in awake Pekin ducks (avg. 2.25 kg) with a pneumotachograph as the change in a 20 L/min bias flow of gas through a compartment sealed around the duck's head. Blood gases were sampled from the brachial artery. Isobaric hypoxia (I) was induced by decreasing $FIO_2$ to 0.13 (n=4) or 0.07 (n=4) at an atmospheric pressure of 750 Torr. Comparable levels of hypobaric hypoxia (H) were achieved in a hypobaric chamber at 480 and 287 Torr ambient pressure. Control measurements were made in normoxia at 750 Torr (N) before and after each hypoxic measurement. Mean results (±sem) were:

| | $PIO_2$(Torr) | $PaO_2$(Torr) | $PaCO_2$(Torr) | $\dot{V}E$(L/min) |
|---|---|---|---|---|
| N | 144.7(0.2) | 102(.9) | 32.1(1.5) | .89(.07) |
| H | 88.2(.1) | 56.3(1.4) | 26.2(0.7) | 1.24(.13) |
| I | 90.7(.5) | 57.9(1.4) | 26.9(1.3) | 1.25(.07) |
| H | 48.4(.2) | 31.8(1.4) | 10.5(0.3) | 2.89(.84) |
| I | 48.4(.2) | 29.4(2.6) | 12.1(0.9) | 2.00(.14) |

We conclude that the reduced gas density associated with hypobaria comparable to 3,800 m does not significantly affect gas exchange in hypoxic resting ducks. At higher altitudes ventilation increases more than if density was constant but arterial blood gases are similar. Supported by NIH POI H217731-11.

64.6

OXYGEN CONSUMPTION RATES, CARDIAC OUTPUT, AND VENTRICULAR dP/dt DURING HYPOTHERMIA WITH DIFFERENT pH STRATEGIES. David C. Willford, Esther P. Hill, and Francis C. White. UCSD, La Jolla, CA 92093; and San Diego VAMC, La Jolla, CA, 92161

We studied 14 hypothermic (29°C) immature domestic pigs, with half (7) maintained with constant pH approximately 7.4 as they were cooled, and 7 using the alpha-stat pH strategy (pH= 7.51 at 29°C). The animals were anesthetized with halothane, ventilated, and instrumented to measure blood gases, cardiac output ($\dot{Q}$), oxygen consumption ($\dot{V}_{O_2}$) by the Fick equation, and maximum positive left ventricular dP/dt.

| | Temp. °C | pH | $\dot{Q}$* | $\dot{V}_{O_2}$* | dP/dt ** | |
|---|---|---|---|---|---|---|
| pH-stat | 29.4 | 7.36 | 70.0 | 4.92 | 2518 | *ml/min/kg |
| mean S.E. | 0.1 | 0.01 | 6.0 | 0.41 | 285 | |
| alpha-stat | 29.2 | 7.51 | 69.3 | 3.58 | 1598 | **mmHg/sec |
| mean S.E. | .2 | 0.01 | 12.9 | 0.26 | 132 | |

Temperature and cardiac outputs did not differ between the groups, but $\dot{V}_{O_2}$ and dP/dt were significantly higher in pH-stat group than in the alpha-stat group ($P < .02$). Since it has been suggested that alpha-stat acid-base regulation maintains metabolic integrity better than pH-stat acid-base regulation, we hypothesize that the increased $\dot{V}_{O_2}$ and left ventricular dP/dt are due to a sympathetic response to a perceived acidosis in the pH-stat animals. Supported by NIH Grant HL-17731 and a Grant from the Veterans Administration.

64.7

THE RELATIONSHIPS BETWEEN THE REGULATION OF BLOOD pH AND BODY TEMPERATURE IN HYPERCAPNIC RODENTS. A. Bar-Ilan* (Spon: S. Cassin), Dept. of Zoology, The Hebrew University, Jerusalem, ISRAEL, and Dept. of Pharmacology, University of Florida, College of Medicine, Gainesville, FL 32610.

Arterial blood acid-base status was measured in unanesthetized, unrestrained guinea pigs, albino rats, rabbits, nutrias, and sand rats exposed to various levels of hypercapnia (0%, 10%, and 14.5% $CO_2$ in air) for up to 6 hr. Oxygen consumption ($\dot{V}O_2$) was measured in an open flow system. Rectal temperature ($T_b$) was measured using a thermistor. The decrease in blood pH after 1 hr of exposure to $CO_2$ was linearly correlated with the change in $T_b$: $\Delta$ pH = 0.023 $\Delta T_b$ - 0.246; r = 0.937. The changes in $\dot{V}O_2$ did not always follow the pattern of changes in $T_b$; e.g., for the guinea pig, a $\Delta T_b$ of -2.4° C was accompanied by a $\Delta \dot{V}O_2$ of -27%; whereas for the sand rat, a $\Delta T_b$ of -3.5° C was concurrent with a $\Delta \dot{V}O_2$ of +35%. An inverse linear relationship was found between the whole body buffer value ($\lambda = -\Delta \log PaCO_2/\Delta$ pH) and $\Delta T_b$; higher $\lambda$ values were found in species that showed small $\Delta T_b$ values during exposure to hypercapnia. Lowering of body temperature was previously reported to be accompanied by a reduction in the ventilatory sensitivity to $CO_2$, an increase in blood pH, and a decrease in metabolic production of $CO_2$. A controlled lowering of $T_b$ during exposure to hypercapnia may thus be one mechanism involved in the physiological adaptation of mammals to elevated carbon dioxide in burrow atmosphere.

64.8

**THE EFFECT OF BILATERAL VAGOTOMY ON THE VENTILATORY RESPONSE OF SNAKES DURING CO2 UNLOADING.** **Ronald K. Gratz. Michigan Technological University, Houghton, MI 49931.**

**Previous work has shown that snakes (genus Nerodia) hyperventilate during steady state CO2 breathing and that this response is eliminated by bilateral vagotomy (Gratz, Am. J. Physiol. 246:R221-R227). In the present study, I have found that immediately after the snakes are returned to room air breathing following CO2 breathing, they hyperventilate considerably above the level seen during steady state CO2 breathing. This hyperventilation is caused by a markedly elevated respiratory rate, something not seen during steady state CO2 breathing. At this time arterial PCO2 is still elevated but lung gas PCO2 has returned to the control value. Bilateral vagotomy markedly reduces the hyperventilation during this period of CO2 unloading. I conclude that peripheral, vagal afferent receptors somehow inhibit the full hyperventilation response to steady state CO2 breathing.**

64.9

VENTILATION AND LUNG OXYGEN EXTRACTION IN THE BAT PHYLLOSTOMUS HASTATUS ACUTELY EXPOSED TO SIMULATED ALTITUDES FROM 0 TO 11 KM. Steven P. Thomas, Ann T. Farabaugh & Dian B. Thomas Dept. Biol. Sci., Duquesne University, Pittsburgh, PA 15282

Although birds are generally much more tolerant of acute high-altitude (hypoxic) stress than are nonflying mammals, little information is available in this area for bats. We have measured steady-state metabolic rate and ventilation from bats fitted with flow probes as they rested quietly inside an open-circuit chamber at 23.4°C and 742.5 torr. Altitudes from 0 th 11 Km were simulated by mixing $N_2$ and air in various ratios using a digital gas blender. Some pooled data (n=15) from the three bats studied (mean mass = 97.7 g) follow:

| Km | MO2 | f | Vt | VI | EL |
|---|---|---|---|---|---|
| 0 | 171.3 | 84.6 | 1.3 | 88.0 | 0.24 |
| 11 | 113.8 | 150.0 | 1.7 | 253.0 | 0.24 |

Metabolic rate (MO2, uMol O2/min) decreased linearly with increasing altitude. Minute ventilation rate (VI, $cm^3$ BTPS/min) increased modestly from 0 to 6 Km, but then increased dramatically primarily as a result of an increase in breathing frequency (f, b/min). Lung oxygen extraction (EL) attained a maximal value of 0.33 at 8 Km, and was equal to its sea level value at 11 Km. This bat's tolerance to acute hypoxic stress is clearly superior to that of a typical nonflying mammal, and compares favorably to those reported for some birds. These results support the thesis that both mammalian and avian respiratory adaptations for flight can serve as preadaptations for withstanding acute hypoxic stress. (Supported by NSF Grant DCB-8303050).

64.10

THE INFLUENCE OF VENTILATORY STATE ON INTRACARDIAC SHUNTING IN THE TURTLE, Pseudemys scripta. Fred N. White, James W. Hicks* and Atsushi Ishimatsu* Abteilung Physiologie Max-Planck Institut fuer Experimentelle Medizin, Goettingen, F.R.G.

Periodic breathing in reptiles is associated with a pronounced cardiorespiratory coupling, with heart rates being maximum during ventilation. During apnea a bradycardia developes associated with an increase in pulmonary vascular resistance. In order to examine the effects of these events on levels of intracardiac shunting, seven turtles were chronically implanted with four cannulae (right and left atrium, pulmonary artery and right or left aortic arch) an allowed to recover for 48 hours at 15 C. Blood samples were drawn from all sites during ventilation and three periods during apnea (5-10 min, 15-20 min and 25-30 min) and analyzed for PO2, PCO2 and pH. Using the Fick approach, the magnitude of intracardiac shunting was determined for each sample period. Levels of shunt were also determined by using microspheres. During ventilation the %R-L shunt was 23± 8 ($\bar{x}$ ± SD) and increased to 71 ± 28 during the first 5-10 min of apnea. The levels of R-L shunt remained large throughout apnea. This is in contrast to the microsphere results which showed relatively large and unchanging values during both ventilation and apnea.

64.11

CALCIFICATION AFTER MOULT IN THE BLUE CRAB: ION TRANSPORT AND HORMONAL CONTROL. James N. Cameron* (SPON: J.L. Larimer) The Univ. of Texas, Marine Sci. Inst., Port Aransas, TX 78373

Almost no mineral salts are conserved when the Blue Crab (Callinectes sapidus) moults: during the 7 to 14 days following the moult, the new carapace is mineralized with $CaCO_3$. In the 24 hr after the moult, the following processes change from nearly zero to very high rates: calcium uptake from seawater, to as high as 20 mEquiv/kg-hr; bicarbonate uptake, from slightly negative to as high as 16 mEquiv/kg-hr; $H^+$ excretion, from about zero to the same range. Transport of all three ionic species, $Ca^{++}$, $HCO_3^-$ and $H^+$, is active, influenced by concentrations of ions in the blood and external medium, and not driven by changes in the trans-gill electrical potential, which stays constant at 3 mV, inside positive. Lowering of the external [$Ca^{++}$], e.g., stops calcification, reduces blood [$Ca^{++}$], and is fatal at values less than 4 mM. Crustacean steroid hormones do not appear to be involved in the switching on of these responses. Injections of ecdysone or eyestalk extracts from various moult stages have no influence on calcium metabolism. Moult and the post-moult calcification proceed normally in eyestalk-less crabs. Preliminary results indicate that there are changes in the pattern of peptides in the blood of various moult stages. Work in progress is directed toward investigating the role of peptide neurohormones in the control of the post-moult calcification process. [Supported by NSF Grant PCM83-15833 to the author.]

64.12

KALURESIS INDEPENDENT K HOMEOSTASIS IN DOGS: CEPHALIC AND B RECEPTOR INFLUENCE AFTER NEPHRECTOMY: Lloyd W. Chapman, Nathan Hiatt, Mayer B. Davidson* and Jonathan Hiatt.* Cedars-Sinai Medical Center, Los Angeles, California 90048: UCLA Medical Center, Los Angeles, California 90024.

In control nephrectomized (nephx) dogs infused with 2 mEq KCl/kg/hr until prelethal ECG changes appear, the development of hyperkalemia (and cardiotoxicity) is delayed by activity of a kaluresis independent K homeostasis mechanism (K transfer capacity) that transports about 70% of administered K to intracelluar fluid (ICF). With the addition of either propranolol blockade of B receptors or ligation of the major brain arteries, K transfer capacity is 33 and 42% respectively. With the addition of both B blockade and artery ligation, K transfer capacity rises to 59% - nearly that in controls. However, the effect of simultaneous pancreatectomy (pancx) differs. In control K loaded nephx dogs (unimpeded blood flow to the brain and active B receptors) K transfer capacity is 67% after pancx; in K loaded nephx dogs with artery ligation and blockaded B receptors, K transfer capacity falls 10% after pancx. A reciprocal relation between insulin and B receptor mediated K transfer can explain the findings.

64.13

MECHANISMS OF HYPO-OSMOTIC REGULATION IN A EURYHALINE CRAYFISH. Michèle G. Wheatly, Univ. of Florida, Gainesville FL 32611

Ion regulation was examined in Pacifastacus leniusculus acclimated in FW (hemolymph maintained hyperosmotic), 350 mOsm SW (isosmotic) and 750 mOsm SW (hypo-osmotic). In FW, $Na^+$ and $Cl^-$ fluxes were respectively 336 and 686$\mu$ equiv $kg^{-1}h^{-1}$. The antennal gland (kidney analogue) reabsorbed 95% of electrolytes from the primary filtrate therefore minimizing urinary efflux. The TEP was 18 mV blood negative. In 750 mOsm SW $Na^+$ and $Cl^-$ fluxes trebled. Ion substitution experiments confirmed that 50% of the flux was via exchange diffusion, and that the branchial epithelium had greater cationic permeability. Urine flow rate decreased to 1/6 in isosmotic solution and was negligible in 750 mOsm SW. Measured TEPS suggested that $Na^+$ was distributed passively while $Cl^-$ was actively extruded in 750 mOsm SW agreeing with the teleost model for salt extrusion. Significant $Na^+/K^+$ dep ATPase activity (around 15 nmol Pi.mg protein $^{-1}$. min $^{-1}$) was found in the antennal gland as well as the gills not only in FW animals but also in hyporegulating crayfish implicating its involvement in ion excretion. Specific activity in isosmotic media was minimal. (Supported by NSF grant PCM 84 15373)

64.14

ACID-BASE BALANCE AND IONOREGULATION IN RAINBOW TROUT: DUAL EXPOSURE TO LOW ENVIRONMENTAL pH AND HIGH EXTERNAL SALINITY. *Elizabeth Lee Hofmann.* University of Toronto, Toronto, Ontario, Canada, M5S 1A1.

Adult rainbow trout were cannulated and exposed to an environmental pH of 4 for 4 days. To study the forces affecting the net flux of ions across the gill, the external [NaCl] was raised to alter the gradient for passive diffusive loss of NaCl. Therefore tests were run at two different concentrations, 40mM and 100mM NaCl. In the former, trout showed significant losses of plasma [$Na^+$] and [$Cl^-$] and increases in blood [$H^+$]. In 100mM NaCl, plasma [$Na^+$] and [$Cl^-$] remained stable in both experimental and control animals. Although some increase in plasma [$H^+$] was evident these results were inconclusive because of the high variability seen in control values. However, while control values for net base excretion were similar at both salinities, a significant difference was found at pH 4. At 40mM NaCl the mean value showed a net loss of base from the animal while at 100mM this loss was reversed. This was accomplished through a significant increase in $NH_3$ excretion. This may provide support for a $Na^+/NH_4^+$ or $Na^+/H^+$ ion exchange mechanism.
(Supported by Canadian National Sportsmen's Fund and Natural Sciences and Engineering Research Council, Canada).

64.15

ELECTRICAL RESPONSES OF HOLOTHURIAN MUSCLE. Robert B. Hill. Department of Zoology, University of Rhode Island, Kingston, R.I. 02881

Spontaneous contractions of a segment of isolated muscle of Holothuria cinerascens are initiated by asynchronous spiking, which leads to a gradual depolarization. The time course of the depolarization, which underlies the spiking, is parallel to the time course of the subsequent contraction. Bursts of large spikes precede a rapid phase of contraction. Spontaneous contractions are not propagated across a sucrose gap. Caffeine contractures are not accompanied by depolarization, and contractility is lost in a series of caffeine contractures. Depolarization with KCl temporarily restores the contractility lost in a series of caffeine contractures. Both acetylcholine and KCl induce overall depolarization and correlated force, but in low concentrations of acetylcholine individual muscle units may depolarize independently, perhaps indicating differing sensitivities.

64.16

BODY TEMPERATURE, SPRINT SPEED. AND MUSCLE CONTRACTION KINETICS IN LIZARDS. A.F. Bennett, R.B. Huey and Henry B. John-Alder. Univ. California, Irvine; Univ. Washington; Rutgers Univ.

Burst running speeds were measured in 11 species of Australian skinks of diverse thermal preferenda ($T_P$) at body temperatures ($T_B$) from 15 to 40°C. Speed is strongly dependent on $T_B$ between 15 and 25°C (mean $Q_{10}$ = 2.4, range 1.7-3.8) but relatively thermally independent at higher $T_B$: 80% of maximal speed is achieved over a $T_B$ range of 8.0-11.0°C in all species. The temperature at which maximal speed is attained ($T_O$) is significantly correlated with $T_P$ ($T_O$= 26.4 + 0.25$T_P$, p<.025) but is not equivalent to it (regression slope≠1.0). Consequently, cryophilic species perform less well at $T_P$ than do thermophilic species: thermophilic genera ($T_P$>29°C; Ctenotus, Egernia, Leiolopisma, Sphenomorphus) have bursts speed >90% of maximal at $T_P$; cryophilic genera ($T_P$<25°C; Eremiascincus, Hemiergis) attain only 50 - 75% of maximal speed at $T_P$. The limitation of skeletal muscle twitch kinetics on limb cycling frequency and burst speed is examined. Supported by NSF Grants PCM81-02331 and DCB85-02218 to AFB.

65.1

THE EFFECT OF HISTAMINE BLOCKERS ON VASCULAR ENDOTHELIAL LANTHANUM ($La^{3+}$) BINDING. S.A. Barman*, J.T. Saari and M.D. Olson*. Departments of Physiology and Anatomy, University of North Dakota School of Medicine, Grand Forks, ND 58202.

Using ionic lanthanum ($La^{3+}$) as an electron opaque marker for calcium ($Ca^{2+}$) binding sites in the isolated rabbit heart, we have previously shown via transmission electron microscopy (TEM) that the $Ca^{2+}$ channel blocker verapamil inhibits $La^{3+}$ binding to the plasma membranes and plasmalemmal vesicles of vascular endothelial cells and that histamine enhances $La^{3+}$ (i.e. $Ca^{2+}$) binding in the presence of verapamil. We concluded that if histamine enhances microvascular permeability via an endothelial cell contractile response as proposed by other investigators, the response may be mediated by an enhancement of $Ca^{2+}$ binding to the cell membrane. In this study, we attempted to determine whether $H_1$ and/or $H_2$ receptor mediation is involved in the $La^{3+}$ binding effect of histamine. We infused diphenhydramine, an $H_1$-receptor blocker, or cimetidine, an $H_2$-receptor blocker, into isolated perfused rabbit hearts prior to cumulative infusions of (in order) histamine, verapamil and $La^{3+}$. TEM analysis revealed both antagonists attenuated the histamine-induced $La^{3+}$ binding to the plasma membranes of vascular endothelia. This evidence suggests the effect of histamine on $La^{3+}$ ($Ca^{2+}$) binding is mediated via both receptor types, which is consistent with the hypothesis that histamine's regulation of microvascular permeability may involve both receptor subtypes. (Supported by NIH Grant HL28217 and UND Office of Research and Program Development)

65.2

HISTAMINE CONSTRICTS LYMPHATICS IN THE DOG FORELIMB. J.M. Dabney, M.J. Buehn*, and D.E. Dobbins. Department of Physiology, Uniformed Services University, Bethesda, MD 20814-4799.

Infused or endogenously released histamine increases the permeability of small blood vessels and dilates arterioles but its effect on lymphatic vessels is not well-described. We measured the pressure in a small lymphatic in the paw of the anesthetized dog when the vessel was perfused in situ with artificial lymph containing histamine. Blood to the forelimb was pumped at constant flow while measuring perfusion pressure. Small artery and small vein pressures in the paw, right atrial and systemic arterial pressures were also measured. Histamine was infused into the lymphatic at concentrations of $1.32 \times 10^{-5}$, $1.32 \times 10^{-4}$, and $1.32 \times 10^{-3}$ molar of base. Lymphatic perfusion pressure was not changed by $1.32 \times 10^{-5}$ M histamine but was increased from a control of 7 to 11 mmHg by the $10^{-4}$ dosage. A further increase to 13 mmHg occurred with $10^{-3}$ histamine. No significant changes in systemic arterial pressure, right atrial pressure or the vascular pressures in the forelimb were produced by infusions of histamine into the lymphatic. It should be noted that the effect of each dosage of histamine was determined on a different group of animals. This was necessary because the first infusion of histamine into the lymphatic rendered it unresponsive to any subsequent infusion of histamine. However, the vessels did respond to other constrictors. These studies indicate that lymphatics of the dog forelimb are constricted by histamine but only to an initial exposure. (Supported by USUHS grant #C07680)

65.3

RECEPTOR MEDIATION OF MICROVASCULAR RESPONSES TO SEROTONIN N.L. Alsip*, P.D. Harris, and A.S. Luebbe*. Dept. Physiology, Univ. Louisville, School of Medicine, Louisville, KY 40292.

Serotonin (5-HT) constricts large arterioles (> 50 μm) and dilates small arterioles (< 50 μm) in skeletal muscle. Our study attempted to identify the receptors which mediate this differential microvascular response. In anesthetized rats, the cremaster muscle (with intact nerve and blood supply) was secured in a Krebs-filled tissue bath, controlled for pH, $PO_2$, $PCO_2$ and temperature. Vessel diameters were measured via videomicroscopy. Serotonin, added directly to the tissue bath, caused a constriction of large arterioles (significant at $10^{-5}$M) which was attenuated by cyproheptadine (CPH, $10^{-5}$M) and methysergide (MS, $10^{-7}$M), two non-specific 5-HT antagonists; as well as by LY 53857 ($10^{-8}$M), a specific 5-$HT_2$ blocker, but not by phentolamine (α-blocker, $10^{-4}$M). In addition, 5-HT caused a dilation of small arterioles (significant at $10^{-6}$M) which was blocked by CPH and MS (non-specific 5-HT blockers) but not by LY53857 (5-$HT_2$ blocker, $10^{-5}$M), diphenhydramine (histamine blocker, $10^{-5}$M), propranolol (β-blocker, $5 \times 10^{-6}$M) or mefenamate (prostaglandin synthesis inhibitor, $4 \times 10^{-5}$M). These data indicate that 5-HT induced constriction in the microcirculation is mediated via 5-$HT_2$ receptors, whereas 5-HT induced dilation of small arterioles appears to be mediated by 5-$HT_1$ receptors. Thus, it appears that 5-$HT_1$ receptors have a role in hormonal control of the smaller arterioles. Supported by Amer. Ht. Assoc., KY Affil.

65.4

THE EFFECT OF SEROTONIN ON PROTEIN EXTRAVASATION IN THE CORONARY MICROCIRCULATION. James M. Reynolds* and Paul F. McDonagh. Dept. of Physiology, Texas Tech Health Sciences Center, Lubbock, Tx. 79430

Platelet release products may modulate vascular permeability. To determine the effects of serotonin (5-HT) on transcoronary protein extravasation, isolated rat hearts were perfused at constant flow with a Krebs-albumin solution to which either 5-HT or saline (PBS) was added via a sideline. The final concentration of 5-HT in the perfusate was $10^{-6}$ M. Transcoronary extravasation of FITC-BSA (O:I ratio), coronary pressure (P), flow per gram (Q), and cardiac water content (W:D ratio) were measured. Coronary vascular resistance (R) was calculated as R=P/Q. We found:

| | Q | $R_{20}$ | $R_{60}$ | O:$I_{40}$ | W:D |
|---|---|---|---|---|---|
| PBS | 1.40±0.11 | 35±5 | 57±16 | 0.57±0.02 | 5.6±0.2 |
| 5-HT | 1.43±0.08 | 56±9 | 51±7 | 0.50±0.02 | 5.5±0.2 |
| P | NS | <0.05 | NS | <0.05 | NS |

After 20 min of perfusion, the R of the PBS group was lower than that of the 5-HT group. Although R often increased later in the experiment in the PBS group, that of the 5-HT group remained stable. We observed a significant decrease in protein extravasation in the 5-HT group. This decrease may be due to vasoconstriction, reduced fluid convection, or a direct effect on vascular permeability. (Supported by NIH HL32330 and NIH HL07289.)

65.5

ENDOTHELIAL CELL DEPENDENT VASODILATION IN RESISTANCE VESSELS. Sharon S. Kelley* and Harvey V. Sparks. Michigan State University, East Lansing, MI. 48824.

We tested the hypothesis that the vasodilator response to acetylcholine (Ach), ATP, and adenosine (Ado), but not isoproterenol (Iso) is endothelial cell (EC) dependent in the blood perfused, canine hindlimb. The role of EC in vivo was further examined by testing the hypothesis that exercise hyperemia is mediated by an EC dependent mechanism(s). We used methylene blue (MB) and 5,8,11,14 eicosatetraynoic acid (ETYA) to inhibit endothelium dependent vasodilation of resistance vessels. There was no significant effect of time or saline vehicle on the flow dose response curve (drc) to Ach, ATP, or Iso (n=5). The Ach and ATP drc were shifted to the right in a parallel fashion in the presence of MB (n=5, $p<.05$) whereas the drc to Iso was not affected. ETYA shifted the Ach dose response to the right and had no effect on Ado or ATP drc (n=5). Ethanol, the vehicle for ETYA, had no effect on Ach drc, although it appears to shift both ATP and Ado drc to the right (n=3). At an oxygen consumption of 3.0ml$O_2$/m/100g both MB (n=5) and ETYA (n=5) reduced free flow exercise hyperemia, but had no effect on blood flow at oxygen consumptions of 6 or 10. The vehicles ethanol (n=3) and saline (n=5) had no effect on exercise hyperemia. The results of this study suggest a role for EC mediated vasodilation in resistance vessels and a possible role for EC in exercise hyperemia at low oxygen consumption. Supported by USPHS HL25779.

65.6

THE SYSTEMIC AND PULMONARY EFFECTS OF SODIUM PENTOBARBITAL ON ALPHA-ADRENERGIC BLOCKADE. M.G. Espejo* and W.H. Drummond. Univ. of Florida, Gainesville, FL 32610

The interactive effects of sodium pentobarbital (Pento) and an alpha blocking agent, phentolamine (Ph) were investigated in 10 chronically instrumented lambs. We implanted vascular and atrial catheters, a pulmonary arterial flow transducer and ligated the ductus arteriosus. After recovery, we infused 22 mg/kg of Pento or an equal volume of saline (Na) on alternate days, followed by 2 mg/kg of Ph, then 0.2 mg/kg of methoxamine (M). Mean systemic (SAP), pulmonary artery (PAP), and left atrial pressures (LAP), cardiac output/kg (CO), and heart rate (HR) were recorded 30 minutes after Pento infusion, 20 minutes and 10 minutes after Ph and M infusions respectively. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated. The peak response to M analyzed by using a two way repeated measures ANOVA is shown below:

| | SAP | SVR | PAP | PVR | LAP | CO | HR |
|---|---|---|---|---|---|---|---|
| Pento | 74.8±5.4 | .68±.14* | 27.0±3.1* | .23 ±.04* | 1.4±.66 | 141±19* | 258±17* |
| Pento+Ph+M | 67.1±4.7** | .70±.24** | 24.3±2.5 | .20 ±.05* | 1.0±.56 | 161±25 | 288± 8 |
| Na+Ph+M | 62.3±3.2 | .53±.13 | 24.8±2.8 | .17 ±.04 | 1.7±.85 | 166±23 | 297± 9 |
| Pento vs Na | NS | NS | NS | S | NS | NS | NS |

*p < .05 Compared to Baseline **p < .05 M response compared to Pento + Ph alone

SAP and SVR increased similarly in both Pento and Na groups after M. The increase in SAP in the Pento group was associated with an increase in SVR, not CO. PVR increased after M, in the Pento group vs. the Na group. Thus Pento attenuated the hypotensive response to Ph and accentuated pulmonary vascular tone.
Supported by the American Heart Association.

65.7

Reduced peripheral beta-adrenergic responsiveness in diabetic rats. M.J. Katovich, C.A. Sninsky* and K. Marks*, Depts. Pharmacodynamics and Medicine, University of Florida, Gainesville, FL 32610.

Peripheral beta-adrenergic responsiveness was investigated in male Sprague-Dawley rats 4 weeks after diabetes was induced with streptozotocin (65 mg/kg). Serum glucose was increased significantly in the diabetic rats as when compared to controls. Six diabetic and six control rats received a chronic carotid cannula to allow for continuous measurement of blood pressure and heart rate in free-moving, unrestrained animals. Following administration of isoproterenol (5 ug/kg, sc), the fall in mean blood pressure and the elevation in heart rate were significantly greater in the controls than the diabetic rats. These differences were apparent 3 min. following administration of isoproterenol and were maintained for 25 min. Mean tail skin temperature (TST) responses to isoproterenol was also assessed in the diabetic rats. Baseline TST were similar in both groups. TSTs were elevated in the control rats by 2, 3 or 5$^{0}$ C following the 25, 40 or 100 ug/kg doses of isoproterenol, respectively. However, there were no changes in TST observed in the diabetic rats in any of the studies. Collectively, these data suggest that the peripheral beta-adrenergic system is markedly depressed in streptozotocin-induced diabetic rat. This reduced responsiveness may be related to the adrenergic neuropathy reported in these rats. (Supported by NIH HD 18133 and a Diabetes Research Development Award).

65.8

BETA-ADRENERGIC RECEPTORS: SUBSTRATES FOR PHOSPHORYLATION BY RHODOPSIN KINASE ? Suleiman W. Bahouth* and Craig C. Malbon. Department of Pharmacolgy-HSC, SUNY at Stony Brook, Stony Brook, New York 11794-8651

Adaptation, the diminished response of a biological system to the continued presence of a stimulus of constant magnitude, is observed in phototransduction as well as activation of adenylate cyclase by beta-adrenergic catecholamines. Phosphorylation has been implicated as a possible mechanism for the adaptation that occurs in both phototransduction and catecholamine-induced desensitization. Rhodopsin kinase phosphorylates the bleached photopigment rhodopsin. The ability of rhodopsin kinase to phosphorylate the beta-adrenergic receptor (Mr = 65 kDa) was examined utilizing rhodopsin kinase prepared from bovine retina rod-outer-segments. Basal membranes of human placenta with 4-5 pmol of receptor /mg of protein were incubated with a kinase preparation, $\gamma$-labeled [$^{32}$P]ATP, EDTA, EGTA, and the presence and absence of the beta-adrenergic agonist isoproterenol. In the presence of agonist a Mr = 65-kDa peptide of the membranes was phosphorylated. Propranolol, a beta-antagonist, blocked the labeling of this peptide observed in the presence of agonist. These data suggest the possibility that beta-adrenergic receptors and rhodopsin are homologous with respect to recognition by rhodopsin kinase. Supported by USPHS grant AM25410 from the NIH.

65.9

**THE EFFECT OF NATIVE CANINE HEARTWORM (DIROFILARIA IMMITIS) INFECTION ON FEMORAL ARTERY VASOREACTIVITY IN VIVO.** Lana Kaiser & Harvey V Sparks Jr., Michigan State University, East Lansing, Michigan 48824

Canine heartworm is a major cause of morbidity in domestic dogs. The adult parasite is known to alter pulmonary artery morphology and in vitro vasoreactivity. We noted that dogs with native heartworm infection often had depressed femoral artery endothelial cell dependent responses. Experiments were designed to test the hypothesis that heartworm infection adversely affects in vivo femoral artery endothelial cell dependent responses. We used pentobarbital anesthetized dogs; 7 with native heartworm and 4 noninfected controls. A femoral artery-jugular vein shunt was created and shunt blood flow controlled by a clamp on the tubing. Phasic and mean femoral artery diameter was measured by sonomicrometry. Endothelial cell dependent dilations to acetylcholine (ACH) and maximum flow and nonendothelial cell dependent responses to norepinephrine (NE) and sodium nitroprusside (SNP) were evaluated. Heartworm dogs showed constriction at low concentrations of ACH and a right shift in the ACH dose response curve (ED50: $5.5 \times 10^{-4}$ vs $3.1 \times 10^{-5}$M). Heartworm depressed maximum NE constriction (0.32±.04 vs 0.54±.06mm), but did not alter maximum dilation to SNP (0.42±.07 vs 0.45±.09mm). The ability of the femoral artery to dilate to maximum flow was inversely correlated with the total female worm burden (r=-.75). Adult Dirofilaria immitis may release substance(s) that adversely influence the reactivity of distal vascular segments. (Supported by USPHS # HL 25779)

65.10

EFFECT OF TEMPERATURE ON DEGRADATION OF NOREPINEPHRINE IN RABBIT EAR ARTERY. Michael Roberts, John Chilgren and Mike Huang*. Department of Biology, Linfield College, McMinnville, OR 97128.

We used paper chromatography to study breakdown of NE by the enzymes monoamine oxidase (MAO) and catechol O-methyl transferase (COMT) at different temperatures. Isolated ear arteries were incubated with $^{3}$H-NE at the following temperatures: 9, 16, 23, 30, 37, and 42 C. Degradation was assessed by obtaining chromatograms of two sets of metabolites: those remaining in the vessel following incubation, and those that diffused to the incubation fluid. Metabolites were eluted from the vessels, and the eluate was evaporated to 50 µl in a rotary evaporator. Incubation fluid was studied by withdrawing a 20 µl sample. In both cases, chromatograms were made by spotting on Whatman P-81 paper and developing with distilled water: 95% ethanol: n-butanol (1:1:1). Radioactivity on chromatograms was assessed by liquid scintillation counting. Degradation of $^{3}$H-NE was less than 10% at 9 and 16 C, and increased to 30% at 42 C. Metabolites of NE remained in the vessel at temperatures below 23 C. At 23 C and above, diffusion of metabolites to the incubation fluid was proportional to temperature. The metabolites 3-methoxy-4-hydroxy-phenylethylglycol (MP) and 3-methoxy-4-hydroxymandelic acid (VM) appeared only at the higher temperatures. This suggests either that the B form of MAO has its thermal optimum at a higher temperature than the A form, or that MP and VM can be formed only after COMT has degraded NE to normetanephrine. At high temperatures, degradation may be a significant factor in disposition of NE. Supported by NIH Grant HL-29551 and American Heart Association (Oregon Affiliate) Grant-in-Aid.

65.11

MYOGENIC RESPONSE TO COOLING IN THE CENTRAL EAR ARTERY OF THE RABBIT. C.T. Harker and P.M. Vanhoutte, Department of Physiology and Biophysics, Mayo Clinic, Rochester, MN 55905.

Experiments were designed to investigate the effect of cooling in the central artery of the rabbit ear. Rings were suspended in physiologic salt solution for recording isometric force. When acutely cooled (from 37 to 24°C) a major myogenic response occurred. The magnitude of the response was variable, at times exceeding 50% of the contractile force elicited by a maximal concentration ($10^{-5}$M) of exogenous norepinephrine. Blockade of alpha- and beta-adrenoceptors did not affect the increase in force with cooling. The response was abolished by papaverine ($10^{-4}$M) or incubation in $Ca^{2+}$-free medium (for 3-5 minutes). Depletion of intracellular $Ca^{2+}$ by repeated stimulation ($10^{-6}$M norepinephrine) in $Ca^{2+}$-free medium, followed by replacement of extracellular $Ca^{2+}$, likewise eliminated the response. Treatment with the $Ca^{2+}$-antagonists verapamil ($10^{-5}$M), nimodipine ($5 \times 10^{-6}$M) or diltiazem ($10^{-5}$M) partially inhibited the magnitude of the contraction evoked by cooling. It was unaffected by incubation with tetrodotoxin, alpha-beta-methylene-ATP ($10^{-6}$M), and indomethacin ($10^{-5}$M). The data indicate that the central ear artery of the rabbit exhibits a myogenic response to acute cooling which is mediated by $Ca^{2+}$-stimulated $Ca^{2+}$-release. (Supported in part by grants HL 05883 and HL 07269.)

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1887-1987

# Centennial Update

One of the major commitments of the Centennial Celebration is to use the past as the foundation for examining the present state of physiology and for anticipating the future. To that end, the Centennial Celebration is planning a series of historical talks and displays that will depict the evolution of physiology and of the Society during its first 100 years. Those concerned about the present state of physiology and troubled about its future should take heart from the disquietude that attended its birth and the creative force that emerged from this restlessness.

The Society was organized on December 30, 1887. Physiology was then closely linked to medicine and the controversies at the time of the formation of the Society reflected strong differences in outlook between practitioners of medicine and medical scientists. After attempting unsuccessfully to dominate planning for the AMA-sponsored International Medical Congress that was scheduled to be held in Washington, DC, in 1887, the research-oriented medical specialists organized their own congress in Washington, DC, in 1888. For physiologists to participate they were obliged to form an organization of their own that could operate under the umbrella of the new congress.

The new organization known as the American Physiological Society was not created de novo. On the biological side, APS was an offshoot of the American Society of Naturalists founded in 1883 that, in turn, was an offshoot of the American Association for the Advancement of Science. However, by its formation the American Physiological Society became the first disciplinary society in the biomedical sciences. Strict criteria for membership were adopted from the outset, requiring publication based on original experiments. However, the criteria were somewhat loose with respect to defining who was a physiologist. Indeed, of the twenty-eight charter members, less than half were primarily physiologists. The rest of the group were physiological chemists, pharmacologists, physicians who conducted experiments privately, physiological psychologists, bacteriologists, hygienists, and physiological botanists. Retrospectively, within these diverse elements were the seeds for the formation of many offshoot societies, in particular, the American Society of Biological Chemists (1906) and the American Society for Pharmacology and Experimental Therapeutics (1908). It is not difficult to draw an analogy between the diversity in constituency and uncertainties about the nature of physiology at the time that the American Physiological Society was born and the contemporary scene.

From its beginning in an era of turbulence in the medical profession, the American Physiological Society emerged as a compelling influence that not only shaped the destiny of physiology for a century but contributed importantly to the emergence of other biomedical societies. At the Centennial Celebration, the birth of the American Physiological Society and its 100 years of progress will provide a backdrop for presenting the current state of physiology and its future prospects to members and guests of APS as well as members of offshoot societies.

*Photo*: S. Weir Mitchell, physiologist and neurologist, was said to have initiated the idea of forming the American Physiological Society. One of the foremost medical researchers of his day, he is shown here (*center*) in his Philadelphia clinic in 1890.