THE PHYSIOLOGIST

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A Division of Research in an Academic Clinical Department

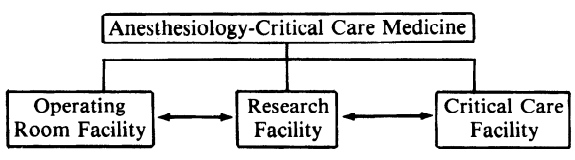
RICHARD J. TRAYSTMAN
Department of Anesthesiology and
Critical Care Medicine
Johns Hopkins Hospital
Baltimore, Maryland 21205

The development of a Research Division within an Academic Clinical Department is technically no different from one that is developed within a straight Basic Science Department. While the underlying purpose of the Research Division in a Clinical Department may be distinctly different from one in a Basic Science Department, many goals are similar. Probably the most important function of a research facility is to perform excellent research. Whether the research done is of a basic science or clinical nature is irrelevant; what is important is that the research be well thought out in its hypothesis, be of sound scientific quality, and utilize valid procedures and techniques. The development of intra- and interdepartmental research programs is also an important function of a Research Division, and the Ph.D. Researcher can be a catalyst in the organization of such research programs. Finally, teaching aspects comprise another area in which the research division may play a major role. This may involve didactic lecturing or direct one-on-one teaching, in the laboratory, of medical students, graduate students, residents, fellows (both post-Ph.D and M.D.), and younger faculty members. This teaching role is probably much more varied for the researcher in a Clinical Department than for the researcher in a Basic Science Department. One of the main roles of the Ph.D. researcher in a Basic Science Department is to participate strenuously in the teaching of medical students and, to some degree, graduate students. Even though the Ph.D. in a Clinical Department may teach in the medical school, it is not a main role. His teaching role is different in that he is more involved in laboratory-type teaching of postdoctoral M.D. or Ph.D. individuals, medical students on elective time, residents, fellows, and young or older clinical faculty. Graduate-student teaching is somewhat limited unless joint appointments are such as to allow graduate students to spend their research time within the Clinical Department.

My own department, Anesthesiology and Critical Care Medicine, is comprised of three distinct autonomous divisions, each with its own director: *1*) an Operating Room facility, *2*) a research facility, and *3*) a Critical Care Facility (Table 1). As a Clinical Department at the Johns Hopkins Hospital, one major role of our Department is to anesthetize patients properly and to ensure their care before, during, and after surgery. The other of our patient-care divisions deals with the care of the critically ill patient. At present the department's involvement in critical care is with the Pediatric Intensive Care Unit and the Surgical Intensive Care Unit. In a certain sense, the Research Division represents the completion of an idea and commitment of our Department and University to academic and intellectual excellence. One of the major roles of the Research Division is to bridge the gap between basic research and clinical medicine by performing research of high quality in both areas. The key aspect revolves around the idea of having M.D.'s and Ph.D.'s working together both in the research laboratory and the clinical facilities. During the first year of operation of our "new" department, it has been relatively easy to entice our M.D. colleagues into the animal laboratory to do research, and many of them have been most successful. Now the efforts are being concentrated on getting our Ph.D. researchers into the clinical facilities to do research, and while this is somewhat more difficult, success is imminent.

As mentioned previously, there are a number of common factors necessary to formulate a Research Division in a clinical or a basic science department. In either case,

Table 1
Departmental Structure and Facilities



26 Operating Rooms	14 Laboratory Spaces	50 Beds
35 Anesthesiologists	7 Physiologists	10 Intensivists
39 Nurses	9 Full-Time Technicians	8 Technicians
15 OR Technicians		100 Nurses (Pediatric and Surgical ICU)

Presented at Symposium on Employment of Physiologist in Academic Departments, APS Fall Meeting, 14 October 1981, Cincinnati, OH.

it is of utmost importance to have complete unqualified support from the Chairman of the Department, Dean of the Medical School, President of the Hospital, or some other individual who is in a strong position to exert such support. Clearly, other factors necessary to ensure the success of any Research Division are an ample supply of funds, space, and equipment and an ability to attract outstanding researchers. Although it is imperative to have excellent people in your Research Division, even they will find it difficult, if not impossible, to produce excellent work without appropriate financial support and facilities. This again is where support from the Chairman is absolutely necessary. In this case, there must be adequate funds, space, and equipment to support the basic scientist's needs as well as those of the clinical faculty who utilize the animal laboratories to do research.

With respect to my own research division at the present time, the support funds arise from several sources. We are heavily indebted to the National Institutes of Health (NIH) and the American Heart Association (AHA). Our research is supported through these agencies by individual research grants or parts of program projects or center grants. We have also been fortunate in that some of our young faculty have young (new) investigator awards to provide salary support. The wisdom of our Departmental Chairman in channeling departmental funds toward research efforts is of critical importance, for it allows individuals within the department who do not yet have grant support an opportunity to be involved with research. Many of these individuals are full-time Anesthesiologists or Intensive Care Clinicians who play key roles in bringing those funds into the department in the first place. One of the important philosophies of our department is that our clinical faculty will have a given amount of protected time for research activities (usually 1–2 days a week). In fact, at the present time, we will not consider hiring a full-time Anesthesiologist or Intensivist unless they are willing to spend that much time in the research laboratory. This can be either clinical or basic research; nevertheless, the intellectual stage is set for both our clinical and research faculty. The hope here is that departmental funds can support research activities until individual research grants can be obtained from NIH or AHA. Another excellent source of funds within our University System is the University itself. Our University provides to any young faculty member (via competitive grant application) a modest sum of money for pilot or preliminary experiments over a one- to two-year period. Though the amount of these funds is not overabundant, they are quite sufficient for the purpose of purchasing experimental animals and supplies.

Two other sources of research funds relatively unique to clinical departments are drug companies and alternative private donors. In clinical departments, where work with patients is common, drug trials are important. It is especially interesting for the researcher who is working directly in the area of interest of the drug company. For example, our group is involved in mechanisms of cerebral vasodilation. Some drug companies are interested in finding an appropriate cerebral vasodilator to be used in stroke patients or following cerebral vasospasm. With our interest and expertise in cerebral blood flow mechanisms, both in animal and human populations, we would be perfectly suited to working with a company having similar interests. With respect to other private sources, many patients and patients' families who have been helped by our department, either from the Anesthesiology or Intensive Care point of view, are generous with their own personal funds and wish to see their financial gifts utilized in scientific research. Clearly these sources of funds are unique to a clinically oriented department and can be used in a variety of ways.

Concerning the development of intra- and interdepartmental research programs, it is of importance to begin intradepartmental programs first. In our research division, all of our research (Ph.D.) faculty are trained cardiovascular, cardiopulmonary physiologists. It is of importance that each researcher develops his own research program, be productive (i.e., grants and publications), and provide a good intellectual environment for the entire Research Division. Once their own programs are clear and progressing well, intradepartmental research efforts can be established, both between researchers and between researchers and clinicians. Following the success of intradepartmental programs, interdepartmental programs can be established between departments. For example, at the present time, our Research Division has active research programs with a number of other departments, and not all of them are within the Johns Hopkins Hospital surroundings. Our collaborative efforts with the Cardiology and Respiratory Divisions at the Johns Hopkins Hospital, the Respiratory Division at the Baltimore City Hospitals, the Environmental Physiology and Toxicology Division of Environmental Health Sciences at the School of Hygiene and Public Health, the Perinatal Division, the Pediatric Surgery Division, and the Neurology and Neurosurgery Divisions at Johns Hopkins Hospital provide important research and intellectual support of a clinical and basic science nature. These interdepartmental relationships allow for the combined efforts of enormously talented individuals toward basic and/or clinical research for the intended good of the patient. They allow for combined research programs, program projects grants, center grants, and so forth, and allow for the treatment of patients via a combination of clinical and research professionals. As a result of these intra- and interdepartmental relationships both basic and clinical research of a wide spectrum can be done. For example, ongoing projects in our research group range from the role of oxygenases in the control of cerebral blood flow and metabolism to the role of collateral ventilation in health and disease.

From my point of view, as a physiologist, I find the atmosphere of a Clinical Department extremely exciting, productive, and challenging. There are literally unlimited opportunities for both basic science and clinical research and for collaboration with clinicians and researchers of varied backgrounds, again for the ultimate good of the patient. It is, in a certain sense, a "Physiologists' Disneyworld," for collaboration with Clinicians and Researchers alike allows high-quality research and teaching of any kind to be done both in the animal laboratory and in the patient care facilities. What more can a good physiologist ask for?

A Physiology Chairman's Objectives in Selecting Young Faculty Members: Criteria in a Smaller Medical School Setting

JAMES P. FILKINS
Department of Physiology
Loyola University of Chicago
Stritch School of Medicine
Maywood, Illinois 60153

My assignment in this second symposium organized by the Career Opportunities in Physiology Committee of the American Physiological Society is to share with you some views on how a chairman selects young faculty members for a Department of Physiology. Since the large multidisciplinary state medical school is covered elsewhere, my focus will be relative to the smaller medical school.

By its nature, a smaller school has certain unique features that influence the selection of faculty. The total number of full-time faculty lines is 8 to 10 vs. the 20 to 30 lines in the larger school setting. Due to the small size, each appointment is especially important to the "critical mass" needed for research and educational efforts. A smaller department has its primary undergraduate teaching commitment to medical students. Indeed, at the Stritch School of Medicine of Loyola University, medical students are our only undergraduate assignment. Due to this relatively restricted teaching role, our faculty must be competent and prepared to assume medical teaching assignments; i.e., there is no opportunity to develop lecture skills in dental, nursing, or other undergraduate courses. Also, a smaller department generally has restricted space and facilities; thus some types of very high demand research programs simply cannot be accommodated.

Selection of a young faculty is based on ability to function in three fundamental areas of academic responsibility—research, teaching, and service. Some general characteristics for each faculty function will be presented, and the unique features of each will be considered for a smaller school setting.

Criteria to Assess Research Competence of a Young Faculty Candidate

Table 1, based on T. M. Saba's presentation at the First Career Opportunities Symposium, summarizes some characteristics that weigh heavily in the assessment of the research potential of a young faculty member. In contrast, Table 2 presents the negative aspects of a research assessment, i.e., rejection criteria. Speaking from the positive perspective, a young faculty candidate should *1*) exude motivation and interest in research; *2*) demonstrate a strong desire for independence; *3*) have skills in hypothesis formulation and in experimental design; *4*) have a reasonable track record of publications in quality refereed journals; *5*) be prepared to write a competitive research grant proposal; and *6*) demonstrate a willingness to work extra hours, a resiliency to bounce back from setbacks, and an ability to accept and profit from constructive criticism. The interested reader should consult Saba's article for elaboration of these criteria, especially for both positive and negative characteristics relating to research capabilities.

Certain additional considerations also weigh into the research criteria as applied to a smaller department (Table 3). Since the faculty must share a common interest to achieve a critical mass for a focus of excellence, it is important to consider the "goodness of fit" with candidates. For example, at Stritch our Department of Physiology is focused on the physiology of cardio-

Table 1

Characteristics of Typical Junior Faculty Member Who Will Be Most Likely To Develop an Independent Research Program

1. Highly motivated and enthusiastic about biomedical research
2. Well-trained to be independent with postdoctoral research
3. Ability to formulate new hypothesis
4. Ability to write a focused grant with supportive data
5. Ability to design well-controlled and realistic experiments
6. Familiar with current literature and techniques
7. Willing to accept constructive criticism from established faculty
8. Capacity to work "extra hours" in a competitive profession
9. Willing to accept failure and "try again" with reference to grants
10. Has published scholarly papers in peer-review journals

From: Saba, T. M. *Physiologist* 24(6): 16–20, 1981.

Table 2

Characteristics of a Typical Junior Faculty Member Who May Have Difficulty in Developing an Independent Research Program

1. Not highly motivated toward experimental research
2. Trained to be supportive rather than independent
3. Limited experience in writing a grant
4. Difficulty in designing a well-focused proposal
5. Difficulty in writing full manuscripts for publication
6. Questions the value of postdoctoral research experience
7. Limited knowledge of current investigative techniques
8. Views basic science career as not competitive or too competitive
9. Prefers committee responsibilities to research
10. Difficulty in assuming multiple tasks, i.e., teaching, research, and service

From: Saba, T. M. *Physiologist* 24(6): 16–20, 1981.

Presented at Symposium on Employment of Physiologists in Academic Departments, APS Fall Meeting, 14 October 1981, Cincinnati, OH.

Table 3
Unique Features of Research in a Smaller School

1. Faculty must share common interest in order to achieve critical mass for a focus of excellence
2. Department must be able to accommodate the applicant's research needs—equipment, space, facilities
3. Sharing of research ideas, technical skills, and common facilities
4. All faculty must have active programs—no room for deadwood

vascular regulation and the pathophysiology of circulatory shock. Therefore, the research competence of the faculty candidate should relate in the broad perspective to the departmental theme. This criterion is especially critical in a smaller department where multiple themes cannot be maintained. It would be folly to recruit an individual who has research talents but no critical peer group for support and critique of his/her research program.

Due to the physical limitation of a small department, an additional criterion of some importance is the ability to meet the space and facility needs of the young physiologist. In a small department, there is generally no room for the "empire builder" or the "million-dollar man or woman"; i.e., a candidate who needs a huge space allocation and a large start-up budget for highly specialized equipment. In a small department, there must be a sharing of research ideas, technical skills, and common facilities. Thus an additional criterion is the total personality of the candidate and the ability to function in an environment that strives for the ideals of a community of scholars. Due to the small number of faculty lines, it is impossible to survive with any "deadwood." Thus the strong commitment to maintain an active research program rather than to specialize into either teaching and/or administrative functions is a most important criterion.

Criteria to Assess Teaching Competence of a Young Faculty Candidate

Table 4 lists a few characteristics that serve as key criteria in the evaluation of the faculty candidate most likely to develop into an effective teacher of medical students. First and foremost, the candidate must possess a solid foundation in medical physiology; i.e., he or she must know organ-system physiology. Too many recent Ph.D. graduates are highly competent in their research areas but simply lack even a textbook knowledge of organ physiology, which is still the essence of a good medical physiology course. It is tragic if a faculty candidate who may have extensive training in cardiovascular physiology feels inadequate to assume responsibility for a lab group or a tutorial session on renal, pulmonary, or gastrointestinal physiology. While "on-the-job" training is obviously going to occur, it is foolish to recruit a candidate who lacks the fundamentals of basic organ physiology.

The candidate must have a sincere interest and indeed a real enthusiasm for medical education. Small academic departments are not research institutes, and medical education is still their raison d'être. Many an honest candidate will admit to having no desire to handle the frustrations of teaching medical students. In contrast, a suitable candidate will manifest an infectious enthusiasm for teaching and true desire to enjoy the classroom. An important criterion is the past teaching experiences of the candidate. A candidate who has had positive successful experience as a lecturer, lab instructor, or conference leader will generally bring a positive attitude to his or her teaching responsibilities and carry them out with a high degree of competence.

A candidate must also possess well-developed communication skills, both verbal and written. This is fundamental to success as a teacher, and there is no substitute for the ability to command attention of a class, to articulate concepts and facts clearly, and to organize presentations in an intellectually stimulating and interesting fashion. Table 5 lists the negative aspects of the teaching characteristics, i.e., rejection criteria.

From the considerations of a small department, additional aspects relative to teaching are of high concern (Table 6). *1*) The candidate must be prepared to assume medical teaching assignments initially. There is often no opportunity to "break in" with the nurses or pharmacists. This is a foolish idea, but it still exists among some candidates for faculty positions. *2*) The candidate must be capable of teaching in different areas. In a small department, rotation of lecture assignments is desirable and often necessary due to sabbaticals, sickness, and so forth. In addition, since lab groups and conferences deal with the breadth of physiology, a solid foundation of knowledge is once again critical to success. *3*) The candidate should be sufficiently talented and flexible to adjust to the unique features of individual departments;

Table 4
Characteristics of a Faculty Applicant Who Will Be Most Likely to Develop into an Effective Physiology Teacher for Medical Students

1. Sincere interest in medical education
2. Knowledge of medical physiology—foundation in organ systems
3. Positive successful experience as a lecturer, lab instructor, or conference leader
4. Well-developed communication skills—articulate, commands attention, organized, clarity

Table 5
Characteristics of a Faculty Applicant Who Will Most Likely Not Develop into an Effective Physiology Teacher for Medical Students

1. Not interested in medical students
2. Not well-founded in medical physiology
3. Has had negative experiences as a lecturer, lab instructor, or conference leader
4. Lacks communication skills—boring speaker, mumbles, scared of class, disorganized, confusing

Table 6
Unique Features of Teaching Medical Students in a Smaller School

1. Assume medical lecture assignments initially
2. Capable of teaching in different areas
3. Accept unique features of departmental program—intensive animal laboratory series, oral examinations, tutorial duties

e.g., at Stritch we have an intensive animal laboratory experience, we require an oral comprehensive examination of all medical students, and we offer abundant tutorial and special help sessions. If a candidate cannot cope with animal labs, oral exams, or tutorial teaching, he would not function well in our program. Similar unique considerations exist in other departments; e.g., a bioengineering approach, highly developed computer-assisted instruction, and no animal labs.

Criteria to Assess Service Competence of a Young Faculty Candidate

The third dimension of a faculty member is the ability to function in service or administration in the Department, the School of Medicine, and the University. All divisions of the educational enterprise require faculty service on various committees, task forces, and governance groups. Some general characteristics of a candidate who will be able to function in this aspect of the profession of the academic physiologist are listed in Table 7. Even though these characteristics seem quite agreeable, anyone in an administrative role will relate to how commonly they are lacking in faculty members. Most chairmen are especially sensitive to the ability of a candidate to share the service load and do not want faculty who are above the pedestrian tasks of running the Department, the School, and the University.

The small department has unique features that influence the selection of faculty (Table 8). All faculty must accept service assignments: small departments have many committees, tasks, and so forth to fill and fewer faculty to fill them. In a small department, the personnel interactions are close: a good criterion of a candidate's "people-handling" skills is the ability to interact with all levels of the chain of command—superior, peers, and subordinates.

Finally, a candidate must be prepared to accept the tradition of the individual department; e.g., at Stritch we have weekly faculty meetings, we are committed to shared decision-making, and we operate on the principle that if a faculty member is given the responsibility for a service function, he then has the authority. Other departments have different traditions and operating styles, but the criterion of how a candidate would function in serving the community within the Department, the School, and the University is as important in the long run as research and teaching criteria.

Table 7

General Characteristics of a Faculty Member Who Will Most Likely Develop into an Effective Administrator

1. Conscientious
2. Good communicator
3. Meets deadlines
4. Appreciates order, hates chaos
5. Appreciates need for planning

Table 8

Unique Features of Administration/Service in a Smaller Department

1. Numerous committee assignments for fewer faculty
2. Interact well with all levels of personnel
3. Adjust to departmental traditions—regular faculty meetings, shared decision-making, responsibility with authority

Concluding Remarks

This presentation has stressed the criteria to evaluate the general characteristics of a faculty candidate who should function successfully in the three major professional commitments of an academic physiologist, namely, research, teaching, and service. In addition, some unique features of the three fundamental functions in a small school setting have been presented. It should be emphasized that these criteria are a chairman's objective and may not be agreed upon by all chairmen. Lastly, no attempt has been made to discuss how these criteria are evaluated; i.e., how a department conducts its screening, search, interviews, and final selection. This topic may be appropriate to a future symposium of the Career Opportunities Committee.

Announcements

Annual Meeting
Society for Industrial Microbiology

The 1982 annual meeting of The Society for Industrial Microbiology will be held August 8–13 at the University of Minnesota, St. Paul, MN. The program will include symposia on Agricultural Biotechnology, Biotechnology of Pharmaceuticals and Health Care Products, Biotechnology of Chemical Products, Process Development for Biotechnology, Genetics of Food Microorganisms, and Subsurface Microbiology. *For more information contact:* Ann Kulback, Society for Industrial Microbiology, 1401 Wilson Blvd., Arlington, VA 22209. Telephone: (703)256-0337.

Fourteenth Miles International Symposium on Cell Fusion

The Fourteenth Miles International Symposium on Cell Fusion will be held at Johns Hopkins Medical Institutions, Baltimore, Maryland, USA, June 7–9, 1982. The preliminary program is as follows: Haploid Cell Fusion (Fertilization), Bennett M. Shapiro (Seattle); Protoplast (Plant and Bacterial) Fusion, Edward C. Cocking (Nottingham); Hybridomas, J. Thomas August (Baltimore); Cell Fusion other than Hybridomas, Francis H. Ruddle (New Haven); Plant Cell Fusion, Eugene W. Nester (Seattle); Monoclonal Antibodies, to be selected. A session consists of 5–6 presentations of 20–25 minutes each and concludes with a 50–60 minute discussion moderated by the session Chairman. *For further information contact:* Edward G. Bassett, Ph.D., Symposium Coordinator, Miles Laboratories, Inc., P.O. Box 40, Elkhart, IN 46515. Telephone: (219)264-8460.

SURVEY OF DEPARTMENTS OF PHYSIOLOGY

Association of Chairmen
of
Departments of Physiology

ANALYSIS OF ACDP QUESTIONNAIRE - 1981

Type of Institution:

Physiology Dept. in a *MEDICAL* (94) OR a *NON-MEDICAL (4) school.**

Specify type of school: Veterinary, Dental, Graduate, and Researc
(one of each)

Affilitation: Public (62) OR Private (36).

[1]Faculty Statistics:

Bold numbers equal grand total

Numbers in light italic are the means per department

	Specify Doctoral Degree(s)				Tenure	Non-tenure	Total
	Ph.D.	*M.D.*	*Ph.D./M.D.*	*Other*			
Full-time paid individuals based in your dept.	1090 *11.12*	122 *1.24*	78 *.80*	37 *.37*	826 *8.43*	448 *4.57*	1317 *13.44*
Part-time paid individuals based in your dept.	37 *.37*	7 *.07*	7 *.07*	9 *.09*	15 *.15*	34 *.34*	58 *.59*
Joint appointments, based in another basic science dept., receiving a portion of salary from your dept. ...	20 *.20*	3 *.03*	0	1 *.01*	12 *.12*	4 *.04*	20 *.20*
Joint appointments, based in a clinical dept., receiving a portion of salary from your dept.	23 *.23*	20 *.20*	11 *.11*	1 *.01*	14 *.14*	6 *.06*	51 *.52*
Joint appointments, based in another basic science dept., receiving no salary from your dept.	116 *1.18*	10 *.10*	0	4 *.04*	71 *.72*	24 *.24*	136 *1.39*
Joint appointments, based in a clinical dept., receiving no salary from your dept.	128 *1.31*	147 *1.50*	30 *.30*	5 *.05*	117 *1.19*	69 *.70*	328 *3.35*

[1]In a correctly completed questionnaire, the total of the first four columns (Ph.D., M.D., Ph.D./M.D., and Other) should equal the total of columns 5 and 6 (Tenure, Non-tenure). The total of the first 4 columns, and the total of columns 5 & 6 should be the same figure as recorded in column 7 (Total). On several questionnaires this was not the case, *i.e.* the total of the first 4 columns, columns 5 & 6, and the last column were all different figures. We had no choice but to record the statistics for each questionnaire exactly as stated. This did affect the accuracy of the means per department.

Unfilled Postions:

Please indicate the number of unfilled positions in each rank in your dept.:

Professor	11 (.11)	*Assistant Professor*	52 (.53)
Associate Professor	16 (.16)	*Instructor*	8 (.08)

How many of the unfilled positions are due to:

Retirement?	13 (.13)	*Failure to promote/tenure?*	6 (.06)
Death?	1 (.01)	*Creation of new FTE's?*	21 (.21)
Moving Away?	35 (.35)		

Project number of jr. postions expected to become vacant in the next 5 years due to retirement, new FTE's, etc.

	.33		.40		.44		.29		.31
yr. 1	33	*yr. 2*	40	*yr. 3*	44	*yr. 4*	29	*yr. 5*	31

Graduate Students and Postdoctoral Fellows:

Number of Ph.D. degrees granted in your dept. between 07/01/79-06/30/80 165(1.68)

Number of grad. students currently enrolled in dept. Ph.D. program 1036(10.57

Number of Postdoc. Fellows currently in your dept. 493(5.03)

Number of Fellows completing training between 07/01/79-6/30/80 131(1.34)

Number of vacant Postdoctoral positions 53(.54)

Do you expect the number of Ph.D. degrees granted in the next 5 years to:

Increase	(36)	*#/year* 2.67
Decrease	(12)	*#/year* 1.95
Not change	(46)	

Do you expect the number of Postdoctoral Fellows who complete their training training each year to change over the next 5 years to:

Increase	(32)	*#/year* 2.08
Decrease	(8)	*#/year* 1.38
Not change	(52)	

Do you have a training grant that supports predoctoral trainees? *Yes* (37) *No* (58

Do you have a training grant that supports postdoctoral trainees? *Yes* (41) *No* (54

What number of your predoctoral and postdoctoral trainees are supported by:

(Means per department, with number of departments in parentheses.)	*Predoctoral*	*Postdoctoral*
Training grants?	4.97 (32)	2.8 (35)
Individual federally funded awards?	1.8 (10)	2.45 (33)
Research grants?	3.68 (56)	3.55 (52)
State Funds?	6.41 (38)	1.39 (9)
Private foundations?	1.25 (12)	2.47 (17)
Institutional awards?	3.9 (35)	2.29 (7)
Medical Scientist Training Programs?	2.8 (10)	1.0 (2)
Other? List _____	2.36 (22)	1.5 (6)

Please assess the degree of satisfaction of your graduates in regard to their opportunities in the job market:

Very Pleased (4) Pleased (39) Neutral (17) Disappointed (15)

Very Disappointed (1)

How many postdoctoral students are presently taking additional training because they are unable to find a satisfactory position? 28

Laboratory Teaching: (Means per department, with number of departments in parentheses.)

How many *wet* laboratories do you hold for *medical* students each year? 5.68 (74)

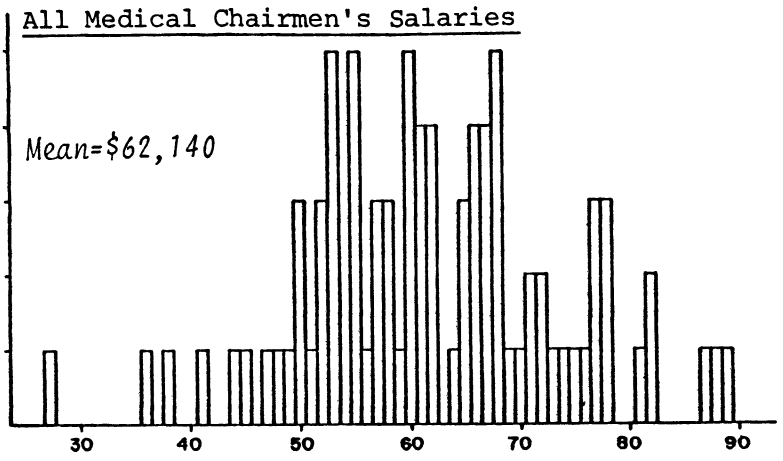
How many *dry* laboratories do you hold for *medical* students each year? 4.86 (58)

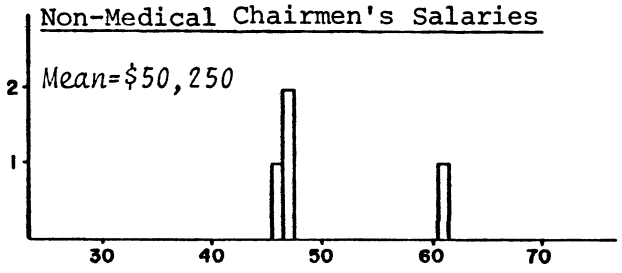
How many *wet* laboratories do you hold for *non-medical* students each year? 13. (59)

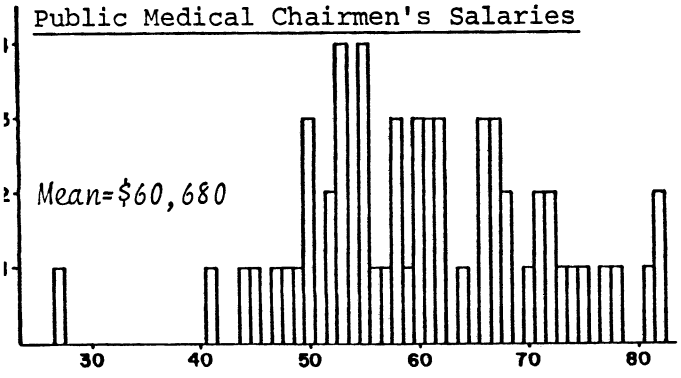
How many *dry* laboratories do you hold for *non-medical* students each year? 9.93 (45)

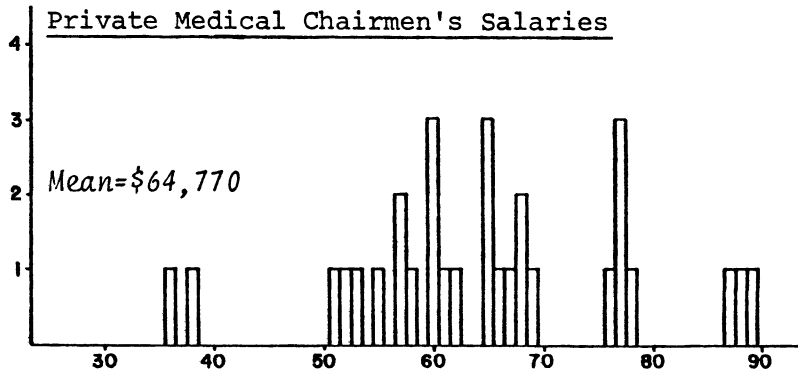
If a good laboratory manual was on the market, would you require your students to buy it? *Yes* (16) *No* (77)

CHAIRMEN'S SALARIES









CHAIRMEN'S SALARIES* (Means)
BY YEARS OF SERVICE

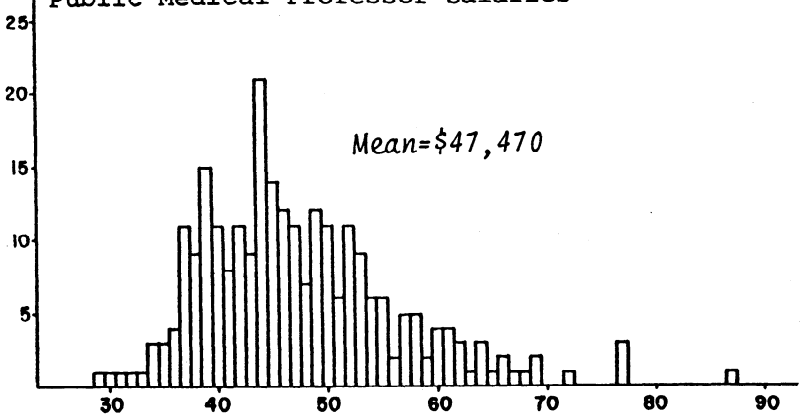
Years of Service	Medical Combined	Public Medical	Range[1] low	high	Private Medical	Range[1] low	high
0-1	57	55	45	67	62	51	69
2	53	53	41	73	—	—	—
3	61	68	27	82	54	38	77
4	58	57	49	66	59	57	60
5	64	60	53	72	70	52	88
6	60	59	55	62	60	60	60
7	62	58	50	66	72	55	89
8	64	64	47	75	66	65	66
9	57	—	—	—	57	57	57
10	65	65	59	71	—	—	—
11	64	67	55	82	59	58	60
12	—	—	—	—	—	—	—
13	74	60	60	60	87	87	87
14	65	60	52	67	76	76	76
15	63	63	53	71	—	—	—
15+	70	68	58	77	71	62	78

*in thousands of dollars

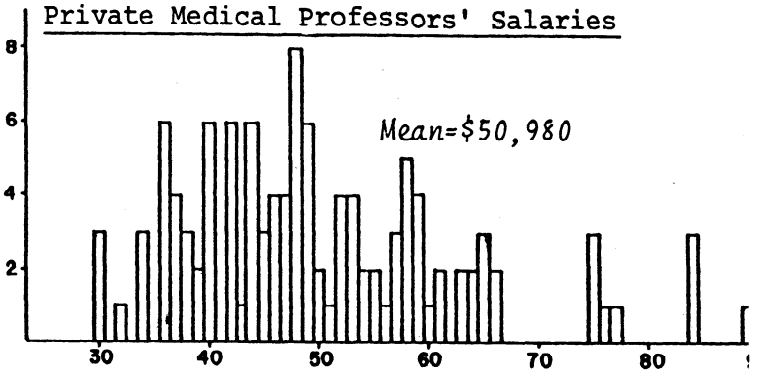
[1]Range is actual expenditure to the nearest thousand.

TEACHERS' SALARIES

Public Medical Professor Salaries



Private Medical Professors' Salaries



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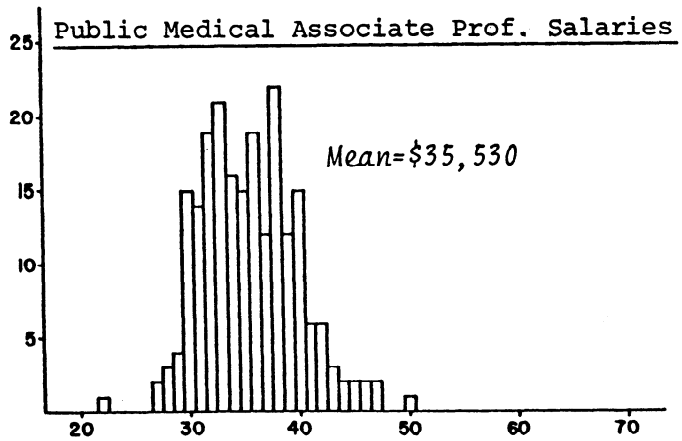

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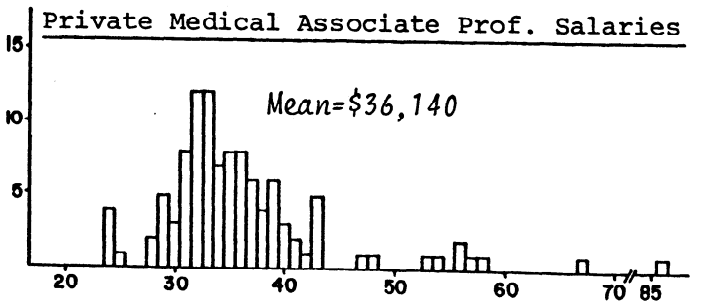
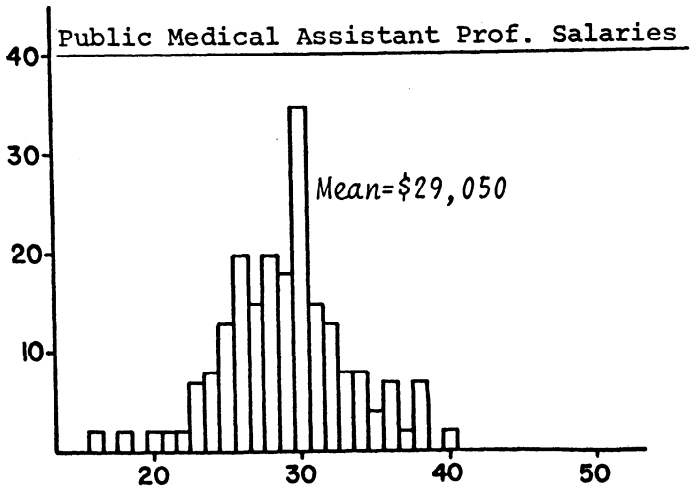


Public Medical Assistant Prof. Salaries



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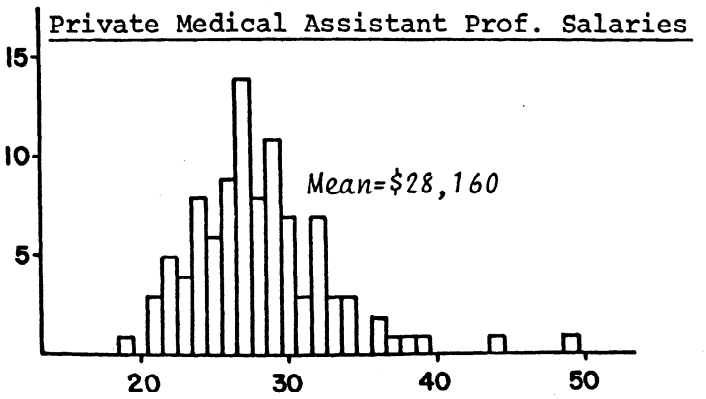
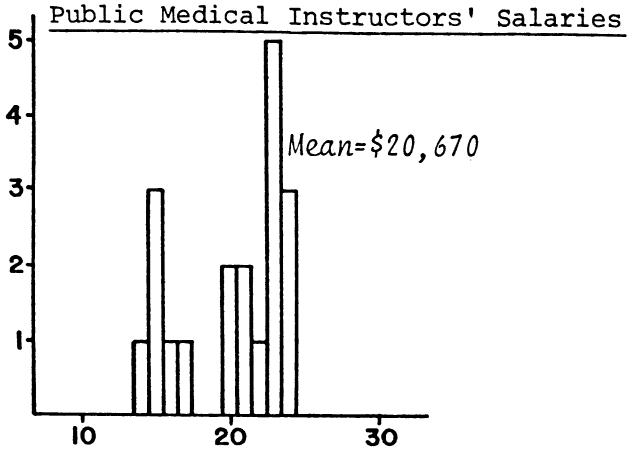
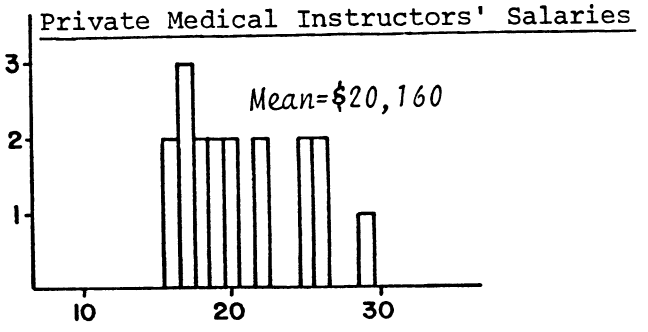






BUDGET[1]

(Mean Expenditure)

	Institutional Sources	Outside Research Grants	Training Grants	Other Budget Support	Total
Private Medical	439,610 (33)	1,025,220 (32)	158,059 (17)	453,640 (14)	1,710,210 (33)
low[2]	235,000	33,000	29,000	6,000	194,000
high[2]	1,366,000	9,449,000	632,000	2,979,000	11,286,000
Public Medical	664,470 (57)	717,810 (54)	120,654 (26)	250,000 (29)	1,557,640 (58)
low[2]	112,000	8,000	15,000	5,000	113,000
high[2]	1,676,000	2,536,000	360,00	2,145,411	4,700,000
Non-Medical	641,000(4)	1,254,000 (3)	38,500 (2)	373,500 (2)	1,774,750 (4)
low[2]	199,000	3,000	27,000	75,000	199,000
high[2]	1,167,000	2,312,000	77,000	672,348	3,300,000
Combined	619,637 (94)	846,413 (89)	131,133 (45)	318,844 (45)	1,680,866 (95)

[1]Actual expenditures of schools reporting funding.

[2]Actual expenditures. "0" amounts were not included in computation of means or in range setting. The number in parentheses is the total number of departments reporting expenditures in that area.

Congress Must Decide Who Will Be Responsible for Animal Welfare Legislation

A question now confronting the Congress in the matter of animal welfare reform is who will be responsible for the enforcement of the Federal laws and regulations that deal with the use of animals.

The Reagan Administration has made its position clear in that it wants to transfer the authority for the primary enforcement of the Animal Welfare Act to the private sector. This proposed change of venue is included in the President Reagan's program to reduce Federal spending.

The private sector, however, has expressed its reluctance to accept responsibility for many of the Federal programs the Administration wants to shed because of already strained budgets at both the state and local levels.

And the Congress, while voicing its concerns last fall about the effectiveness of the U.S. Department of Agriculture in monitoring and enforcing the Animal Welfare Act, now is showing signs of wanting to give Agriculture's Animal and Plant Health Inspection Service (APHIS) another chance.

Under the terms of the Reagan proposal the Administration's plan is as follows.

"To turn the primary enforcement of animal welfare over to states, industry groups, humane societies, and individuals.

"APHIS activities would be aimed at increasing the current level of compliance investigations and prosecution efforts.

"Inspection of regulated dealers, research facilities, exhibits, and carriers, along with the development of procedures for enforcement of the illegal animal fighting ventures provision of the (Animal Welfare) Act, will no longer be handled by APHIS."

This proposed transfer of enforcement and inspection responsibilities to private sector interests is reported by Administration budget officers to represent a savings of $3.4 million in Federal spending in fiscal year 1983. The total expense to the private sector, however, probably would be much more than that amount in terms of the costs of establishing and maintaining the agencies designated for this responsibility.

Although the state governments have stated their concerns about picking up the tabs for federally mandated programs, the Administration does have the support of some of the animal welfare groups for the transfer of inspection and enforcement of the Animal Welfare Act to state and local agencies. This support became evident during recent meetings involving the staff of the House Subcommittee on Science, Research, and Technology; humane organizations and animal rights groups; and scientific societies, including the American Physiological Society.

The representatives from the humane societies and animal rights groups and individual animal welfare activists all pushed for strengthening the current provisions of the Animal Welfare Act by including the representation of animal advocates on all animal research review committees and animal inspection teams. This push for amendments to the Animal Welfare Act is being made as an alternative to the animal welfare reform legislation proposed by Rep. Doug Walgren (D, PA) following the oversight hearings he conducted for the Subcommittee last October.

The opposition by the animal welfare interests to Walgren's proposed legislation is based primarily on the fact that the proposal is limited to only those institutions receiving Federal research support funds, whereas the Animal Welfare Act includes all institutions using animals in research.

By and large, the Walgren proposal represents a compromise of most of the animal reform bills introduced in the House during the first session of the 97th Congress. Some of the amendments to the Animal Welfare Act proposed by Rep. Patricia Schroeder (D, CO) are included as is the emphasis for the development of adjunct methods, proposed by Rep. Robert Roe (D, NJ).

The Schroeder amendments (HR 4406) included in the Walgren proposal would expand private sector accreditation of research institutions to facilities using rodents; involve veterinary science in the design of all research protocols whenever animals are to be used, in the peer review system, and in inspections; and require the reporting of all funds spent for anesthetics and analgesics as well as the dosage used for each laboratory animal.

Roe's proposal (HR 556), which would emphasize the development of adjunct methods, is charged specifically to the Secretary of Health and Human Services in the Walgren proposal and would be supported by appropriation instead of the controversial percentage set aside from all animal research funds.

The proposal to charge the Secretary of Health and Human Services with the responsibility for the development of adjunct methods and the provision for separate funding for this purpose does represent a favorable change.

The Roe bill, originally cosponsored by more than 80 members of the House, was a prime objective of the antivivisectionists. If enacted, a national center for the development of adjunct methods would be established, with its support being allocated by setting aside 30-50% of all Federal appropriations earmarked for research involving the use of animals.

The wisdom of this concept and the method for its support was challenged by the American Physiological Society as well as by other national scientific research associations.

Additionally, the Society has been on record since October as not favoring any new legislation on the use of animals in research, but for appropriation of sufficient funds to improve the activities of APHIS, which have been underfunded.

Ernst Knobil, Ph.D., testifying for the Society at the Subcommittee hearings, told the panel, "The Animal Welfare Act has stringent provisions for overseeing

of animal facilities and . . . no new legislation will provide significant new protection against abuse." He added, "the current activity . . . is indeed woefully underfunded."

The cost of funding the APHIS program to where it can effectively fulfill its role under the Animal Welfare Act has been estimated by Agriculture to be less than $8 million, an amount probably less than what the total cost would be for the state and local agencies.

Whether the Walgren proposal and/or amendments to the Animal Welfare Act are to be enacted by the Congress during this session probably will not be known until a decision is reached regarding the Administration's proposal to transfer the authority for animal welfare enforcement.

In the States

California (Sacramento)—The General Assembly is considering a bill (S 1438) that would prohibit the release of any pound animal for the purpose of research, experimentation, testing, or demonstration.

Florida (Jacksonville)—The City Council is considering a possible repeal of its law permitting the release of pound animals for the purpose of research.

Illinois (Chicago)—An ordinance has been drafted for the City Council that would prohibit the release of pound animals to research institutions; establish a commission to govern the animal shelters; and designate research institutions as catteries and kennels, thus placing them under the governance of the proposed commission.

Missouri (Jefferson City)—Bills (H 1063 and S 509) have been introduced in the General Assembly that would prohibit the release of any animal for the purpose of research. Bills (H 1064 and S 568) also have been introduced that would prohibit the use of live animals in public or private elementary schools and high school.

Colorado (Denver)—A bill being considered by the Colorado General Assembly would make it unlawful to use animals for research, testing, experimentation, or demonstration for scientific, commercial, educational, or other purposes except under certain conditions including certification by the State's Department of Health.

Massachusetts (Boston)—Two bills are before the Massachusetts General Assembly involving the use of animals. One bill calls for the investigation of animal abuse and vivisection by a commission with a mandate that the majority of its members be from animal rights groups. The second bill states that no animal shall be subjected to any scientific investigation, experimentation, or use for medical school or other instruction, or testing of drugs or medicine, if alternative methods are available or the knowledge sought to be gained is available from other scientific data, or if the experiment is repetitive or designed for the purpose of demonstration.

William Samuels

International News

Development of Methods and Recent Advances in Neuroscience

An IBRO-UNESCO Workshop on *"Development of Methods and Recent Advances in Neuroscience"* was held under the auspices of the University of Algiers at the Hotel Aurassi in Algiers, November 13-24, 1981. Professor Clinton N. Woolsey, University of Wisconsin, IBRO Workshop organizer, worked with Professor Mohamud Abdelmoumene, Professor of Physiology at the University of Algiers, to arrange this workshop. In faculty selection Dr. Abdelmoumene was assisted by Professor Denise Albe-Fessard of Paris and Dr. Suzanne Tyc-Dumont of Marseilles in selecting French faculty, and Dr. J.E. Hind aided Dr. Woolsey in selecting an American faculty to cover audition. Thirty-seven faculty members made a total of 67 presentations. The Hotel Aurassi provided facilities for simultaneous translations from French to English and from English to French. About 20 of the faculty took a four-day trip to the Sahara Desert after the Workshop. Already some Algerians are seeking opportunities to receive research training in Europe and the U.S.A.

C.N. Woolsey

Epinephrin(e)

HORACE W. DAVENPORT
William Beaumont Professor of Physiology
The University of Michigan

Every American physiologist has used Adrenalin®, although he probably called it adrenine or epinephrine.

It is a rule that every drug must have at least four names. When the American Cyanamid Company was developing its carbonic anhydrase inhibitors, the in-house name for one was #6063. The compound's designation according to the rules of organic chemistry is *5-acetoamido-1,3,4-thiazole-2-sulfonamide.* The drug was marketed under the registered name of Diamox, but its generic name became acetazolamide. This multiplicity of names is trivial compared with those of the blood-pressure-raising principle of the adrenal medulla. The Merck Index lists 35 names for epinephrine, and the list does not include epinephrin, spelled without the terminal "e" as Abel spelled it when he described his efforts to isolate the compound.

I became interested in the history of epinephrine for two reasons. As a member of the faculty of the Medical School of The University of Michigan, I have been legitimately proud of the fact that in the person of John Jacob Abel, Michigan had the first Professor of Pharmacology in the Western Hemisphere. As a gastroenterological physiologist I knew that Walter B. Cannon began work on the mechanical factors of digestion when he was a first-year medical student at Harvard and that the observations he made in the summer and fall of 1897 led him to a life-long study of the sympathetic nervous system. At the end of his life Cannon attempted to identify epinephrine as the chemical mediator of adrenergic nerve impulses, and he failed. I wanted to understand the reasons for the failure.

In 1894 and 1895 Oliver and Schäfer (1) described the "physiological action of extract of the suprarenal capsules," but they did not give the active principle a name. Neither did their colleague Benjamin Moore (2) when he attempted to determine the chemical nature of the substance. A year or so later John Jacob Abel, the Professor of Pharmacology at the newly opened medical school of Johns Hopkins University, began his effort to characterize what he called epinephrin. On November 5, 1900, Jokichi Takamine (3) applied for a United States Patent on a "Glandular Extractive Product" he called adrenalin, and on April 16, 1901, Takamine (4) was given the right to use the word Adrenalin as a trademark. Later, the trademark was used by Parke, Davis and Company, the Detroit pharmaceutical manufacturers (5). For a while, adrenalin was used to designate the blood-pressure-raising principle without reference to its legal status. For example, Elliott in his famous abstract (6) published in 1904 suggested that "Adrenalin might be the chemical stimulant liberated . . ." by an impulse in a sympathetic nerve. Gradually adrenalin was replaced in scientific papers. Cannon usually used adrenine; sometimes, but not often, he specified that he used the Parke, Davis product when he injected adrenalin (7). As late as 1935 Cannon and Rosenblueth (8) described the effects of injected adrenalin without stating the provenance of the

Cast of Characters

John Jacob Abel

1857	Born
1883	Ph.B., Michigan; student of Vaughan and Sewall
1883–84	Student of Newell Martin at Hopkins
1884–91	Studies physiology, medicine, and chemistry in Germany
1891–93	Professor of Pharmacology at Michigan
1893–	Professor of Pharmacology at Hopkins
1895–96	Begins isolation of epinephrin
1905	Publishes last paper on epinephrin

Jokichi Takamine

1854	Born in Japan
1880–83	Studies chemical engineering in Scotland
1883–90	Works in Japan, in part as chemical engineer
1890–	Comes to the United States; develops and markets Taka-Diastase
1899	Uses Baltimore address
1900(?)	Visits Abel's laboratory at Hopkins
1900	Nov 5: files application for U.S. Patent on adrenalin

Thomas Bell Aldrich

1861	Born
1892	Ph.D., Jena
1893–98	Assistant to Abel at Hopkins
1898–	Employed in Parke, Davis research laboratories
1900–	Isolates adrenalin
1901	Using Takamine's product, he deduces correct elementary formula

Elijah Mark Houghton

1867	Born
1893	Ph.C., Michigan
1894	M.D., Michigan
1894–95	Assistant in Pharmacology, Michigan
1895–	Director of Parke, Davis research laboratories
1900–	Performs assays of adrenalin for Takamine; describes himself as "Lecturer in Experimental Pharmacology, Detroit College of Medicine

compound. Eventually, epinephrine with a terminal "e" became the accepted generic name in America. Some Europeans still use adrenalin. When I was young, I was taught to say adrenalin only when I specified the Parke, Davis product. Otherwise, I should say epinephrine. In addition, a faint air of scandal seemed to hang over adrenalin, something about a stolen secret. No one seemed to know the facts. Tracing the origin of the scandal, if there were one, added piquancy to my investigation.

In this essay I will repeat the name actually used at the time. Thus, in 1900 Takamine said adrenalin while Abel said epinephrin, but Abel, writing in 1927 about 1900, wrote epinephrine.

In 1849 Thomas Addison of Guy's Hospital published a short note in the *London Medical Gazette: Anaemia—Disease of the supra-renal capsules"* (10).In it he described the autopsy findings in three cases. He followed by publishing a 43-page pamphlet in 1855 (11), elegantly illustrated with 11 lithographs, entitled *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules.* He established that the adrenal glands had been destroyed in patients with the characteristic and fatal disease now bearing his name, and he asserted that the adrenal glands are necessary for life. Despite some scepticism, the essentiality of the adrenal glands became an accepted opinion.

George Oliver and Edward A. Schäfer, of University College London, gave papers (1) before the Physiological Society on March 10, 1894, and March 16, 1895, in which they described the "physiological action of extract of the suprarenal capsules." The abstracts are very nearly the summary of a long paper published later in 1895. Oliver and Schäfer confirmed the observation that injection of massive amounts of adrenal extract is fatal to the rabbit, but they found that intravenous injection of a small amount of aqueous or glycerol extract of the adrenal gland causes an immediate and spectacular rise in arterial pressure. Using the classical methods of cardiovascular physiology, they demonstrated that the chief effect of their extract was to cause profound arteriolar constriction and thereby increase peripheral resistance. Oliver and Schäfer asked, "Is the active principle of the gland contained in the cortex or in the medulla?" They concluded that it is only in the medulla and that the faint blood-pressure-raising effects of the cortex could be explained by contamination with medullary material.

Benjamin Moore, a junior colleague of Oliver and Schäfer at University College London, attempted chemical characterization of the physiologically active substance (2). He found that it was not a "proteid," for it readily passed through a dialysis membrane. So did a powerful reducing substance, and Moore at first thought that the reducing substance is the active principle. The reducing substance interested all working on the problem, and its color reactions thoroughly confused the search for the gland's active principle. Its nature was not cleared up until 1928 when Szent-Györgyi (12) isolated hexuronic acid from the adrenal gland as well as from oranges and cabbages. Later hexuronic acid was found to be identical with vitamin C, and there is a problem about priority there too (13).

Although Oliver and Schäfer did not say so, one gets the impression that they and others working on the problem around the turn of the century believed that the blood-pressure-raising principle is the material that makes the gland essential for life. Oliver and Schäfer said, "It must be concluded that one of the main functions, if not the main function [of the adrenal gland), is to produce a material which is added in some way to the blood, and the effect of which is to assist by its direct action upon the various kinds of muscular tissue in maintaining that amount of tonic contraction which appears to be essential to the physiological action of that tissue." Eventually the adrenal medulla, the source of the blood-pressure-raising principle, was shown to be dispensible, and by 1922 Hartman (14) could conclude "that of the two tissues the cortex is the more important." Gaunt (15) said that "others belabored the same question through the 1920's, and finally consensus was achieved that the adrenal cortex was essential for life and that the adrenal medulla was not."

Almost immediately after the publication of Oliver and Schafer's paper, John Jacob Abel, along with many others, undertook to isolate the active principle. Abel had prepared himself well for the task (16). He had graduated from the University of Michigan in 1883, and his Ph.B. degree signified that he had taken the new "scientific" course rather than the older "classical" one. As an undergraduate in the Literary Department, Abel was a student of Victor Vaughan and Henry Sewall, both professors in the Medical Department. Vaughan had been trained as an inorganic chemist, but by the time Abel was his student Vaughan had turned to physiological chemistry and toxicology. Sewall had earned the first Ph.D. in physiology given in the United States as a protégé of Newell Martin at Hopkins. In those days, physiological chemistry was still a part of physiology, and Sewall taught a substantial amount of it in his course on physiology. It may have been at Sewall's suggestion that Abel went to Hopkins to study under Newell Martin, and Martin in turn reinforced Abel's determination to seek advanced training in Europe.

From 1884 to 1886 Abel studied in Carl Ludwig's Physiological Institute in Leipzig where the staff included von Frey, His, and Boehm. The next year Abel went to Strasbourg where the new German Empire had made the university a showplace of German scholarship. There his masters included Kussmaul and von Recklinghausen. When Abel went to Heidelberg his teachers were Erb and Czerny. After returning to Strasbourg for his M.D. in 1888, Abel went to Vienna and then to Bern, intending to learn chemistry to be applied to physiological problems. In the late summer of 1890, Abel received a cable from Victor Vaughan inviting him to become the Professor of Pharmacology at Michigan.

When he was dying of tuberculosis in 1876, Henry Sylvester Cheever, Michigan's Professor of Physiology, wrote to the president of the university telling him what the university must do to promote the science of physiology. He said that the university must establish a separate chair of physiology and that it must give its occupant adequate laboratory space, animal quarters, and time in the curriculum. Cheever, who taught materia medica as well as physiology, said the university must do the same to promote the study of the action of medicines, namely, pharmacology.

It took the university 15 years to act on Cheever's suggestion, and it was Victor Vaughan who made the move. When Dean Palmer died in 1887, Corydon L. Ford, the oldest member of the medical faculty, became the nominal dean. However, Ford left the actual exercise of the dean's powers in Vaughan's hands, so that Vaughan was, in fact, acting dean four years before he became dean by title. As dean, Vaughan's greatest achievement was recruiting a distinguished faculty for Michigan. To fill the chair of pharmacology, Vaughan sought the advice of Schmiedeberg, who recommended Abel. Abel replied to Vaughan's cable by saying that he wanted further training in chemistry. Accordingly, he spent the fall of 1890 in Leipzig working with Drechsel. Then he came to Ann Arbor in January of 1891 to be America's premier Professor of Pharmacology.

With the task of setting up a laboratory from scratch and organizing his teaching, Abel accomplished little research in his two years at Michigan. In 1893 Hopkins, thanks to the Women's Fund, could finally open its medical school, and Dean Welch snatched Abel away from Michigan. At Hopkins Abel was also responsible for teaching physiological chemistry, and in this he was assisted by Thomas Bell Aldrich, who had earned his Ph.D. at Jena in 1892.

Abel first described his method of isolating epinephrin in a paper read before the Association of American Physicians on May 6, 1897, and he published a full description in the July, 1897, issue of the *Johns Hopkins Hospital Bulletin* (17). Abel published another paper in the 1898 volume of the *Bulletin* (18), and on July 14, 1899, he dispatched his definitive paper to Hoppe-Seyler's *Zeitschrift fur physiologische Chemie* (19). These papers, together with a few concurrent abstracts, are the ones upon which rests Abel's reputation for "having isolated the first hormone" (20).

P. D. Armour and Company of Chicago supplied Abel with what must have been a very generous amount of sheep adrenal glands. Abel began by scraping out the medullary portion and drying it on a water bath at 60°C. He ground the residue and extracted it for several days with ether until all fat was removed. After evaporating the ether, Abel repeatedly extracted 100 or more grams of the residual powder with warm water faintly acidulated with sulfuric acid, and then he evaporated the solution to a small volume. He precipitated all proteins with a large excess of strong alcohol, and upon removing the alcohol by distillation, he obtained a brownish fluid. This Abel treated with benzoyl chloride and sodium hydroxide, obtaining a light yellow, tarry benzoyl derivative. He washed the product free of alkali and took up the amber-colored residue in strong alcohol. He boiled the solution with animal charcoal for two hours, and upon evaporating the alcohol Abel obtained a crystalline product.

Abel hydrolyzed the benzoyl derivative in several ways. One was to dissolve it in glacial acetic acid, to heat the solution to near boiling; and then to add an equal volume of hot 25% sulfuric acid. Another was simply to dissolve the compound in a little concentrated sulfuric acid and then to add crushed ice. Later Abel hydrolyzed his compound by heating it with water in an autoclave. Finally, after exhaustive extraction of the hydrolyzed material with either, acetone, and alcohol, Abel obtained his epinephrin as a sulfate, "very active, yet not pure."

In both his second Bulletin paper and in the *Zeitschrift* Abel announced the elementary formula for his compound: $C_{17}H_{15}NO_4$. The data were

	Calculated	Found
C	68.68	69.28
H	6.09	5.05
N	5.00	4.71

T. B. Aldrich left the Department of Pharmacology at Hopkins in 1898 to join the Biological Laboratory of the Scientific Division of Parke, Davis and Company in Detroit. In a paper published in the August, 1901, issue of the *American Journal of Physiology* (21), Aldrich said that in the summer of 1900, working independently, he had been able to obtain a very small quantity of crystalline substance from the suprarenal glands. He wrote, "Before this work could be completed, however, Takamine presented a preliminary paper before the Society of Chemical Industry at its meeting in New York City in the latter part of January [1901]." Takamine described isolation of a compound he called adrenalin, and Takamine's product became available to Aldrich at Parke, Davis. From it Aldrich obtained a sufficient amount of crystalline material for elementary analysis:

	Calculated	Found
C	58.98	57.89
H	7.16	7.33 (misprinted as 7.23)
N	7.65	7.50
O	26.23	27.27

The calculated values are for a compound having the formula $C_9H_{13}NO_3$. This is, in fact, the correct one, but it was some years before Aldrich's formula was shown to be indubitably correct.

Aldrich could obtain a sample of Takamine's adrenalin, because Takamine had a continuing relation with Parke, Davis and Company.

Jokichi Takamine was born in 1854 in the Japanese city of Kanazawa, now called Yokohama (22). His father was a physician who had mastered the Dutch language and through it had learned something of Western chemistry and medicine. The year before Jokichi Takamine was born Commodore Perry had forced his way into Yedo Bay, and in March of 1854 the commercial treaty between Japan and the United States was signed. Consequently, Takamine's youth and early

manhood coincided with Japan's strenuous and successful effort to modernize itself, and Takamine participated to the full in the struggle. Encouraged by his parents, Takamine learned English, and at the age of 17 he entered the College of Science and Engineering, newly established in Tokyo by the Imperial Government. He studied science for six years, all the while supported by a government scholarship. In 1880 he was sent to Glasgow for three years, again at government expense, to study chemistry. Upon returning to Tokyo Takamine was given a post in the Department of Agriculture and Commerce with the duty of applying western science to Japanese industrial problems. In 1884 he was sent by the Japanese government to an international exhibition in New Orleans, and when he returned to Japan he brought with him samples of phosphate rock and the knowledge of the manufacture of phosphate fertilizer. He was sent to Europe and the United States once more in 1887, and with machinery purchased in the United States he subsequently established a factory to produce fertilizer in Japan.

When Takamine returned to Japan from New Orleans he was engaged to marry an American girl, and in 1887 on his way back to Japan from Europe he married her. In 1890, at the bidding of his American father-in-law and with the approval of the Japanese authorities, Takamine returned to the United States with the object of substituting a process he had already developed in Japan for the malt diastase derived from barley that was used in distilling.

Takamine grew an aspergillus fungus, called taka-koji or taka-moyashi in Japanese, upon moistened wheat bran. Bran was a waste product of milling and was cheap. Takamine wrote (23), "The bran of wheat is well sterilized by steam, and then it is thoroughly and carefully inoculated with the spores from the pure culture fungus, and allowed to grow in immense incubators at proper temperature and humidity. In the course of forty-eight hours the bran will be covered with a dense growth of this microscopic plant, and the mass will be found to be rich in diastase, from which it is extracted by percolation with water. The diastase dissolved is now precipitated by the addition of strong alcohol, thus separating it from the mother liquor. The precipitate is now centrifuged and dried, which constitutes Taka-Diastase. It has the remarkable power of converting three hundred times its own weight of starch in ten minutes at proper temperature and condition."

Takamine applied on November 21, 1894, for a patent on his "Process of Converting Starch Material into Sugar" (24).

Takamine's attempt to use Taka-Diastase in the distilling industry was a failure, but operating as The Takamine Ferment Company, he promoted its use in the manufacture of pectin and in bread making. Somehow Takamine also promoted it as a remedy for maldigestion of starchy food, for in 1895 Parke, Davis and Company began to market Taka-Diastase for relief of indigestion (25). For many years the company's catalogs listed 18 preparations of Taka-Diastase, one a mixture of Taka-Diastase, pepsin, and strychnine. The clinical literature of the time contained a few case reports testifying to its effectiveness (26).

Takamine himself publicized Taka-Diastase. In a talk before the Richmond Academy of Medicine and Surgery, given on April 12, 1898, Takamine described the method of production of digestive ferments by microscopical plants (23). When the manuscript of his talk was published in the 1898–1899 volume of the *Virginia Medical Semi-Monthly,* Takamine's address was given as 1431 McCulloch St., Baltimore, Maryland.

I cannot say when Takamine began his attempt to isolate adrenalin. Unlike Abel, Takamine published no progress reports in the form of abstracts and complete papers. He published nothing until he had applied for a patent and a trademark, and then he published a lot. His hero-worshipping biographer wrote (22), "When Abel in 1897 and Otto von Furth [sic] in the year following announced the discovery of epinephrin and suprarenin, respectively, Takamine had already been working on the isolation of the active principle of the suprarenal glands. . . . He was determined to attain the goal which both Abel and von Furth failed to accomplish. Parke, Davis & Co., who had recognized Takamine's creative ability through the success of Taka-Diastase, were keenly interested in this new undertaking of his, and were ready to cooperate with him in a financial way."

Takamine never gave the source of his starting material. He extracted the fat and removed the protein by processes similar to Abel's, but after he had made his concentrated extract with acidified water, Takamine simply precipitated the active principle with ammonia. To purify the precipitate further, Takamine again dissolved it in acid and once more precipitated it with ammonia. This process was accomplished at the latest sometime in 1900, and in a paper published early in 1901 (27), Takamine asserted that he had finished the isolation of adrenalin "last summer," i.e., the summer of 1900. He applied for a United States patent on his "Glandular Extractive Product" on November 5, 1900. The application was divided and refiled, and five United States patents were granted on June 2, 1903. On January 22, 1901, Takamine applied for an English patent that was granted in July of that year (28). In his application filed March 19, 1901, for a trademark on Adrenalin, Takamine said the word had been in use since October 31, 1900 (4).

In addition to filing his patent applications and making his product available to Parke, Davis, Takamine saw to it that his accomplishment became widely known. In addition to the paper given before the Society of Chemical Industry in January of 1901, Takamine gave a paper (29) before the New York State Medical Society in the same month. This latter paper was published immediately in the *Therapeutic Gazette of Detroit.* At the end of it Takamine thanked Dr. E.M. Houghton of Detroit for making physiological tests of his preparation. Takamine sent a paper on "Adrenalin; the active principle of the suprarenal gland" to the *Scottish Medical and Surgical Journal* (30). Takamine and Houghton journeyed together to the 52nd Annual Meeting of the American Medical Association in Minneapolis on June 4–7, 1901. The paper Takamine gave was published the next year in the Association's Journal (27). It was immediately followed by Houghton's paper (31) describing the method of biological assay of adrenalin. The two went to St. Louis for the meeting of the American Pharmaceutical Association on September 16–21, 1901, and they gave the same papers again.

Those were soon published in the *American Journal of Pharmacy* (32).

Houghton had obtained his degree in pharmacy at Michigan in 1893, and therefore he knew Abel. At the head of his papers Houghton described himself as "Lecturer on Experimental Pharmacology, Detroit College of Medicine, Detroit, Mich." That was somewhat disingenuous, for Houghton was, in fact, Director of the Parke, Davis Research Laboratories, and it was not surprising that "Drs. Takamine and Aldrich supplied [him] with a crystalline product from suprarenal glands, which, on comparing its action with the freshly-prepared aqueous extract, proved to be 600 to 800 times as strong. . . ." Houghton's reluctance to identify his employer may have resulted from the fact that in those days pharmacologists working for drug companies were looked down upon by their academic colleagues. When the American Society for Pharmacology and Experimental Therapeutics was founded in 1908 such commercial pharmacologists were not allowed to join.

In those days clinical trials were not hedged by barriers erected by the Food and Drug Administration. When Takamine described the isolation of adrenalin he gave long lists of therapeutic uses. He said that it had already given satisfactory results in the treatment of many diseases: deafness, heart disease, Addison's disease, and exophthalmic goiter. Takamine never said how, when, and where the clinical trials were made, nor did he identify those who made them. Some of the trials may have been conducted by Egerton Yorrick Davis, M.D.

Parke, Davis prepared to market adrenalin at once (25), and by 1903 the company was advertising "Adrenaline-Takamine" in *La Presse Medicale* as "Seul produit authentique préparé sous la direction personelle de son inventeur, le Dr. J. Takamine." Advertisements in the *Journal of the American Medical Association* did not mention Takamine.

The Emperor of Japan conferred the Order of the Rising Sun, Fourth Class, upon Takamine, and he sent 15 Imperial cherry trees to Parke, Davis. The trees were planted in front of the company's administrative offices in Detroit, and they were chopped down during the Second World War (33).

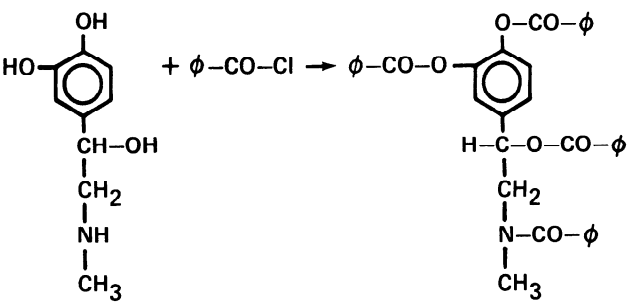
The faint air of scandal hanging over the isolation of adrenalin arises from an interpretation of the relation between Takamine and Abel. More than twenty-five years after Takamine had patented adrenalin, Abel wrote (9), "After I had completed [the investigations described in the *Zeitschrift*] and while I was still endeavoring to improve my process I was visited one day in the fall of 1900 (as I recall it) by the Japanese chemist, J. Takamine, who examined with great interest the various compounds and salts of epinephrine that were placed before him. He inquired particularly whether I did not think it possible that my salts of epinephrine could be prepared by a simpler process than mine." Hartung, in his review of the chemistry of epinephrine (20), paraphrased Abel and continued, "Takamine returned to his own laboratory, prepared concentrated extracts of the glands, and by the addition of ammonia (the base employed by Abel in precipitating his epinephrine) obtained burr-like clusters of crystals." Ordering the facts in this sequence makes it appear that Takamine was successful only after his visit to Abel.

The fall in Baltimore would begin no earlier than September, and if 1900 is the correct date of Takamine's visit to Abel's laboratory, Takamine had already made considerable progress in isolating adrenalin. By October 31 of that year he coined the name adrenalin, and by November 5 he completed the preliminaries for his patent application. It is possible that Abel's memory was at fault and that the visit occurred in 1899. Abel had finished the work described in the *Zeitschrift* by the summer of that year, and Takamine gave a Baltimore address when he published a paper in 1899. In that case he would have had plenty of time, whether or not he had started to isolate adrenalin before he visited Abel.

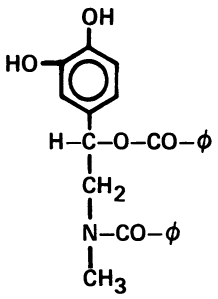
If Takamine had accumulated experience in isolating adrenalin by the time he visited Abel, he was somewhat less than candid when he confined himself to inquiring whether Abel's process might be simplified. Takamine was accustomed to commercial practice with its patents and registered trademarks, and he kept his experience to himself. Abel, accustomed to academic practice in which information was frequently freely exchanged, laid all his data before Takamine. Had Takamine not visited Abel's laboratory, he would still have had adequate information about Abel's methods. By 1900 Abel had published three full-length papers on the subject. A clever chemist, Takamine or Aldrich, could see that somehow Abel had blundered into a morass and that his method did, in fact, need simplification.

Benzoylation was responsible for much of Abel's trouble up to the time of Takamine's visit. Sometime in 1900–1901 Abel realized that the compound he described in the *Zeitschrift*, $C_{17}H_{14}NO_4$, still contained a benzoyl group despite vigorous hydrolysis. Subtracting C_6H_5CO gave the formula $C_{10}H_{13}NO_3$, and Abel continued to believe in that or in a variant, $C_{10}H_{13}NO_3(1/2\ H_2O)$, until he gave up working on the subject. Abel thought that the extra benzoyl group resisting hydrolysis was attached to the nitrogen atom. Hartung (20) said that "the entrance of the benzoyl group into the aromatic nucleus through an adaptation of the Fries rearrangement would account for its nonremoval and probably would not interfere so greatly with its physiological activity. Such a reaction is common with phenols."

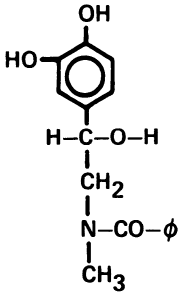
A professor of organic chemistry at The University of Michigan says this is unlikely. When Abel reacted epinephrine with benzoyl chloride, all four reactive groups were benzoylated, the two catechol oxygens, the alcoholic oxygen on the β-carbon, and the nitrogen.



As soon as Abel washed his product free of alkali, the catechol oxygens became protonated and lost their benzoyl groups. One benzoyl group remained at the oxygen on the β-carbon and one on the nitrogen.

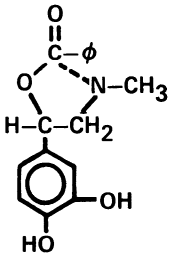


Upon hydrolysis in glacial acetic acid one more benzoyl group was removed, leaving one on the nitrogen atom as Abel thought.



Abel, however, could not get rid of this residual benzoyl group.

It migrated between the nitrogen atom and the oxygen attached to the β-carbon, depending on the acidity or alkalinity of the solution, because the atoms formed a five-membered ring:



If Abel acidified his compound, as he did with glacial acetic acid or sulfuric acid, the nitrogen atom became protonated. The bond between the nitrogen atom and the carbonyl carbon of the benzoyl group was replaced by a bond between the carbonyl carbon and the oxygen atom attached to the β-carbon. If Abel treated his compound with alkali, the benzoyl group migrated back to the nitrogen atom.

Abel's final product had biological activity, but it cannot now be determined whether the benzoylated compound or some contaminant was responsible. Abel had no chromatographic methods for separating components, and he could not tell what his final product contained. At that time no one knew the biological activity of pure epinephrine, and consequently Abel could not make a quantitative assay that might have told him the activity of his product was small compared with that of authentic epinephrine.

Almost from the beginning Abel was engaged in controversy with others who were trying to isolate the active principle (34). One such person was Otto von Fürth of Strasbourg, but the controversy intensified when Takamine and Aldrich published their papers on adrenalin. Abel admitted they had obtained a crystalline material, but he asserted it was not pure. He was critical of Aldrich's formula, $C_9H_{13}NO_3$, and of Takamine's, $C_{10}H_{15}NO_3$. Aldrich replied in an ungenerous spirit. In a paper (35) devoted to proving that adrenalin really is the active principle, he wrote of "epinephrin, and the other questionable products obtained from the gland." Abel replied in kind in the last paper he published on epinephrin (36). That paper is the first one in the first volume of the *Journal of Biological Chemistry,* a journal Abel helped to found. The paper is largely devoted to proving that the correct formula and correct structure of epinephrine are wrong. Abel described his many attempts to isolate epinephrin without benzoylation and without the possibility that the compound might be oxidized, and he reported many elementary analyses of the various products. Abel stuck to $C_{10}H_{13}NO_3(1/2H_20)$, but his last words, actually printed in italics at the beginning of the paper, were *"There is a lack of agreement in the nitrogen content of specimens prepared at different times and from different lots of fresh glands."*

As so often happens, the controversy died out when the controversialists retired from the field and fresh evidence was supplied by others. Takamine did not further work on the chemistry of adrenalin. He became the intermediary between American and Japanese industry, and as such he accumulated a fortune. After 1905 Abel turned to other projects. In 1896 Muhlmann (37) had concluded that "Das Brenzkatechin wird also in der Marksubstanz der Nebenniere gebildet." Abel repeatedly objected to that conclusion, but others agreed that epinephrine is a catechol derivative. In 1903 Pauly, a chemist in Bonn, had recognized that epinephrine must contain an asymmetric carbon atom, and he suggested several configurations for a catechol derivative having Aldrich's elementary formula (38). Almost immediately thereafter both Stolz (39) and Dakin (40) synthesized racemic epinephrine. Both reacted pyrocatechol with chloroacetylchloride to give α-chloroacetophenone. Reaction with excess methylamine gave the methylamino derivative, and reduction produced racemic epinephrine. Stolz used catalytic reduction, whereas Dakin employed electrolytic reduction with lead electrodes. Flacher (41) used (+)-tartaric acid to separate the (−)-isomer from the mixture. In commercial practice the remaining (+)-isomer is racemized and once more resolved. When this process is repeated, almost all the synthetic material can be converted to the physiologically active compound, and the only contaminant of (−)-epinephrine is (+)-epinephrine.

Abel's assertion that Takamine's adrenalin was not pure was correct in a way he did not anticipate: the contaminant of the natural product is norepinephrine (42). U.S.P. Reference Epinephrine, a natural product, was found to contain as much as 36% norepinephrine. Considering the uncertainty of elementary analysis at the time, Abel could not have told the difference between pure epinephrine and the mixture of epinephrine and norepinephrine.

This brings me back to my starting point. About 1930 Cannon began his attempt to identify the chemical transmitter of the sympathetic nervous system (43). He was fairly certain that it was adrenine, but to be on the safe side he called it *sympathin.* His method was to stimulate a peripheral branch of the sympathetic nervous system in a cat and to observe the responses of

organs in the same animal. The organs included the heart, the nictitating membrane, the pupil of the eye, a salivary gland, and the uterus of a nonpregnant cat, and the organs were often sensitized by previous denervation or by a drug. Cannon compared the responses to the circulating transmitter with those elicited by Parke, Davis Adrenalin (8). He soon found that the responses differed depending on the source of sympathin. When the nerves to an organ that is only excited were stimulated, the responses were only excitatory. When the nerves to an organ that is both excited and inhibited were stimulated, the responses were both excitatory and inhibitory. Therefore, Cannon concluded, there are two sympathins, one excitatory and the other inhibitory, which he called sympathin E and sympathin I.

There were two stumbling blocks Cannon could not see *1*) the adrenergic transmitter is, for the most part, norepinephrine and not epinephrine (44); and *2*) the Parke, Davis Adrenalin Cannon used, being the natural product (45), contained norepinephrine as well as epinephrine.

Notes

1. Oliver, G., and E. A. Schäfer. On the physiological action of extract the suprarenal capsules. *J. Physiol. London* 16: i-iv, 1894; 17: ix-xiv, 1895; 18: 230-279, 1895.

2. Moore, B. On the chemical nature of a physiologically active substance occurring in the suprarenal gland. *J. Physiol. London* 17: xiv-xvi, 1895; On the chromogen and the active physiological substance of the suprarenal gland. *J. Physiol. London* 21: 382-389, 1897.

3. United States Patents 730,175; 730,176; 730,196; 730,197; 730,198; 2 Jun 1903.

4. United States Trade Mark 86,269; 16 Apr 1901.

5. The Detroit pharmaceutical concern was Parke, Davis and Company. Sometimes it was carelessly cited as Parke-Davis, but when it became a division of Warner-Lambert Company the latter designation became the correct one.

6. Elliott, T.R. On the action of adrenalin. *J. Physiol. London* 31: xx-xxi, 1904.

7. Cannon, W. B., and H. Lyman. The depressor effect of adrenalin on arterial pressure. *Am. J. Physiol.* 31: 376-398, 1913.

8. One of the many examples, Cannon, W. B., and J. Rosenblueth. *Autonomic Neuro-Effector Systems.* New York: Macmillan, 1937, p. 195.

9. Abel, J. J. Chemistry in relation to biology and medicine with especial reference to insulin and other hormones. *Science* 66: 307-319, 337-346, 1927.

10. Addison, T. Anaemia—disease of the supra-renal capsules. *London Med. Gaz.* 8: 517-518, 1894.

11. Addison, T. *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules.* London: Highley, 1855. (Reprinted in *Medical Classics* 2, no. 3, 1937.)

12. Szent-Györgyi, A. Observations on the function of the peroxidase system and the chemistry of the adrenal cortex; description of new carbohydrate derivative. *Biochem. J.* 22: 1387-1409, 1928.

13. Svirbely, J. L., and C. G. King. The preparation of vitamin C concentrates from lemon juice. *J. Biol. Chem.* 94: 483-496, 1931; King, C. G., and W. A. Waugh. The chemical nature of vitamin C. *Science* 75: 357-358, 1932; Svirbely, J.L., and A. Szent-Györgyi. Hexuronic acid as antiscorbutic factor. *Nature London* 129: 576, 1932.

14. Hartman, F. A. The general physiology and experimental pathology of the suprarenal glands. In: *Endocrinology and Metabolism,* edited by L. F. Barker. New York: Appleton, 1922, vol. 2, p. 119.

15. Gaunt, R. History of the adrenal cortex. In: *Handbook of Physiology: Endocrinology.* Washington, DC: Am. Physiol. Soc., 1975, sect. 7, vol. vi, chapt. 1, p. 1-12.

16. Voegtlin, C. John Jacob Abel, 1857-1938. *J. Pharmacol. Exp. Ther.* 67: 373-406, 1939. I am grateful to Professor John Parascondola for correcting some biographical errors in an early version of this essay.

17. Abel, J. J., and A. C. Crawford. On the blood-pressure-raising constituent of the suprarenal capsule. *Johns Hopkins Hosp. Bull.* 8: 151-157, 1897.

18. Abel, J. J. Further observations on the chemical nature of the active principle of the suprarenal capsule. *Johns Hopkins Hosp. Bull.* 9: 215-218, 1898.

19. Abel, J. J. Ueber den blutdruckerregendes Bestandtheil des Nebenniere, das Epinephrin. *Hoppe-Seylers Z. Physiol. Chem.* 28: 318-362, 1899.

20. Hartung, W. H. Epinephrine and related compound: influence of structure on physiological activity. *Chem. Rev.* 9: 389-465, 1931.

21. Aldrich, T. B. A preliminary report on the active principle of the suprarenal gland. *Am. J. Physiol.* 5: 457-461, 1901.

22. Kawakami, K. K. *Jokichi Takamine.* New York: Rudge, 1928.

23. Takamine, J. Production of digestive ferments by microscopical plants. *Va. Med. Semi-Mon.* 3: 41-43, 1898-99.

24. United States Patent 562,103; 16 June 1896.

25. *Parke, Davis at 100, 1866-1966.* Detroit, MI: Parke, Davis, 1966.

26. For example, Allen, T. H. Notes on Taka-Diastase. *J. Am. Med. Assoc.* 27: 374-375, 1896.

27. Takamine, J. The blood-pressure-raising principle of the suprarenal gland. *J. Am. Med. Assoc.* 38: 153-155, 1902.

28. English Patent 1467; 22 Jan 1901.

29. Takamine, J. The blood-pressure-raising principle of the suprarenal glands—a preliminary report. *Ther. Gaz. Detroit* 16: 221-224, 1901.

30. Takemine, J. Adrenalin; the active principle of the suprarenal gland. *Scott. Med. Surg. J.* 10: 131-138, 1902.

31. Houghton, E. M. The pharmacology of the suprarenal gland and a method of assaying its product. *J. Am. Med. Assoc.* 38: 150-153, 1902.

32. Takamine, J. Adrenalin; the active principle of the suprarenal gland. *Am. J. Pharm.* 73: 523-531, 1901. Houghton, E. M. The pharmacological assay of preparations of the suprarenal gland. *Am. J. Pharm.* 73: 531-535, 1901.

33. Telephone conversation with Dr. Martin L. Black of Warner-Lambert Co., Ann Arbor, MI, 28 Jan 1981.

34. Abel, J. J. On the behavior of epinephrin to Fehling's solution and other characteristics of the substance. *Johns Hopkins Hosp. Bull.* 12: 337-343, 1901; Further observations of epinephrin. *Johns Hopkins Hosp. Bull.* 12: 80-84, 1901; On a simple method of preparing epinephrin and its compounds. *Johns Hopkins Hosp. Bull.* 13: 29-35, 1902; Darstellung und Eigenschaften eines Abbauproductes des Epinephrins. *Ber. Dtsch. Chem. Ges.* 37: 368-381, 1904.

35. Aldrich, T. B. Is adrenalin the active principle of the suprarenal gland? *Am. J. Physiol.* 7: 359-368, 1902; Adrenalin, the active principle of the suprarenal gland. *J. Am. Chem. Soc.* 27: 1074-1091, 1905.

36. Abel, J. J. and R. deM. Taveau. On the decomposition products of epinephrin hydrate. *J. Biol. Chem.* 1: 1-32, 1905.

37. Mühlmann, M. Zur Physiologie der Nebenniere. *Dtsch. Med. Wopchenschr.* 22: 409-411, 1896.

38. Pauly, H. Zur Kenntniss der Adrenalins. *Ber. Dtsch. Chem. Ges.* 36: 2944-2949, 1903.

39. Stolz, F. Ueber Adrenalin and Alkylaminocetobrenzcatechin. *Ber. Dtsch. Chem. Ges.* 37: 4149-4154, 1904.

40. Dakin, H. D. The synthesis of a substance allied to adrenalin. *Proc. R. Soc. London Ser. B* 76: 491-497, 1905.

41. Flächer, F. Uber die Spaltung des sympathetischen *dl*-Suprarenins in seine optisch activ Komponenten. *Hoppe-Seylers Z. Physiol. Chem.* 58: 189-194, 1908.

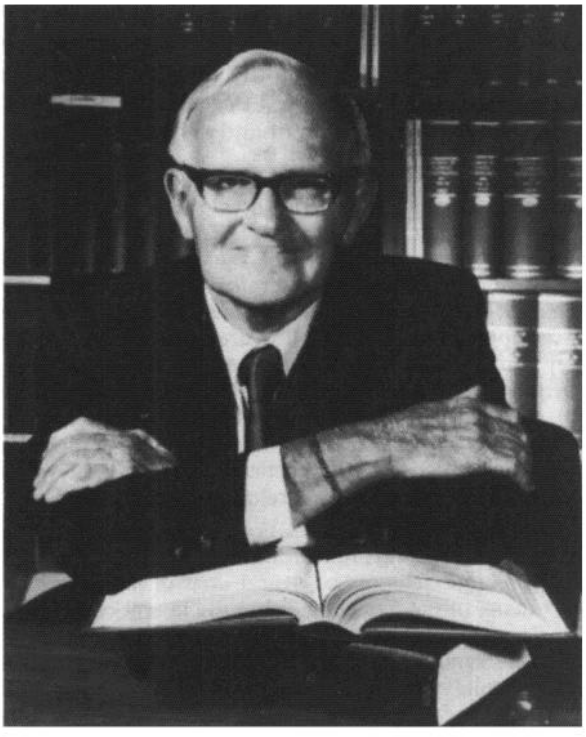
42. Goldenberg, M., M. Faber, E. J. Alston and E. C. Chargaff. Evidence for the occurrence of nor-epinephrine in the adrenal medulla. *Science* 109: 534-535, 1946.

43. Bacq, Z. M. Walter B. Cannon's contribution to the theory of chemical mediation of the nerve impulse. In: *The Life and Contributions of Walter Bradford Cannon, 1871-1945,* edited by C. McC. Brooks, K. Koizumi, and J. O. Pinkston. New York: State Univ. of New York, Downstate Medical Center, 1975, p. 68-83.

44. Euler, U.S. von. Twenty years of noradrenalin. *Pharmacol. Rev.* 18: 29-38, 1966.

45. Parke, Davis did not substitute synthetic adrenalin for the natural product until 13 May 1975. See Ref. 33.

Victor E. Hall



With Victor Hall's death on July 23, 1981, the world of physiology, including innumerable friends and students, lost an inspiring colleague and a spirit of unbounded energy and interests.

Born February 11, 1901, in Victoria, British Columbia, Victor grew up and had his early schooling in that city. Following a year at the Victoria Normal School and a brief enrollment at UC Berkeley, he entered Stanford University where he completed his undergraduate work in 1922, received a Master's degree in physiology in 1925, and obtained his M.S. degree in 1928. From then until 1951 he remained in the Department of Physiology at Stanford, achieving the rank of Professor in 1941.

While at Stanford, Victor Hall developed his major line of scientific research: the metabolic aspects of temperature regulation, in which he inspired students who since have made their own reputations in physiology. He became a member of the American Physi ological Society in 1934.

In 1951 he was invited to UCLA as Professor of Physiology in the nascent School of Medicine, which that year accepted its first class. On the basis of his long experience, Victor was instrumental in developing the physiology course for medical students, as well as the graduate curriculum in physiology. It was largely through his efforts that these evolved into the rigorous and distinguished programs they remain today. His broad knowledge of the scientific literature and his joy in sharing his insights inspired students and colleagues alike. It was fitting that he received the Distinguished Teaching Award at UCLA. Among the many extramural teaching activities that Victor engaged in were several teaching sessions and workshops of the APS in the period 1955–1963.

Victor's international reputation stemmed mainly from his editorship of the *Annual Review of Physiology,* extending from the mid-1940s until his retirement from that post in 1971; under his guidance, it became an indispensable reference for the community of physiologists. In the 1950s, the APS choose Victor Hall as Executive Editor of *Neurophysiology,* the first section of its new Handbook series. He attacked this assignment with his usual vigor and produced a three-volume set that became the standard of excellence and a worldwide reference. Later contributions to the dissemination of scientific information were his chairmanship of the *UCLA Forum in Medical Sciences* and his organization and direction for many years of the Brain Information Service.

All who knew Victor Hall realize that this listing of his scientific teaching and organizational activities leaves untouched the essence of his eminence as an unusual human being. His high spirit and infectious optimism, despite physical disability and numerous illnesses, were a constant source of inspiration. Sensitivity and compassion characterized his relations with all around him.

[A scholarship fund has been established in Victor's memory at UCLA. Friends and colleagues who wish to contribute may send checks, payable to the Regents of the University of California, addressed to Office of the Dean, UCLA School of Medicine, Los Angeles, CA 90024. Such contributions, which should be specified for the Victor E. Hall Scholarship Fund, are tax-deductible.]

Publications Desk

Excitation and Neural Control of the Heart

Excitation and Neural Control of the Heart initiates a new kind of publication for the Society. The preface that the Editors, Matthew N. Levy and Mario Vassalle, prepared describes the content and origin of the book. It is reproduced here.

This book is a compilation of thirteen reviews on the excitation and neural control of the heart. The chapters on cardiac excitation include descriptions of the movements of several ions across the cardiac cell membranes. The latest concepts of the roles of such ion fluxes in the genesis of automaticity and in excitation-contraction coupling are presented. These basic concepts are then applied to the important clinical problem of the genesis of cardiac arrhythmias. Chapters on the development of reentrant circuits, on the effects of myocardial ischemia, and on the relation of repolarization to arrhythmia vulnerability discuss the practical applicability of such fundamental knowledge to the relevant clinical field.

In several of the chapters about cardiac excitation the effects of the autonomic neurotransmitters on ionic fluxes are described; other features of neural control are described in greater detail in the five chapters on the neural control of the heart. In two of these chapters some attention is directed toward the sympathetic and parasympathetic centers in the central nervous system that regulate the cardiovascular system. The other three chapters are devoted to the peripheral mechanisms of neurotransmitter release in the heart and blood vessels. The presynaptic mechanisms involved in peripheral sympathetic-parasympathetic interactions have been investigated intensively during the past several years, and these recent advances are described in detail in the chapters on the peripheral mechanisms.

These reviews are an outgrowth of our tenure as editors of the *American Journal of Physiology: Heart and Circulatory Physiology* from 1977 to 1981. During that period we initiated the policy of publishing a series of review articles on specific themes. Acknowledged authorities from the United States and abroad were invited to prepare the articles. The authors were requested to write the reviews with the aim of bringing the latest information and concepts not only to other workers in their specific fields but also to cardiovascular physiologists with different research interests and expertise. The authors were urged to use a style of writing that would be readily understood by most cardiovascular investigators and students regardless of their specific field of interest. These special articles were reviewed much more extensively than the regular scientific papers submitted to the Journal, to ensure scientific accuracy, balanced interpretation, and clarity of presentation.

The articles were so favorably received by the Journal readers that, with the encouragement and support of the Publications Committee of the American Physiological Society, we had them carefully updated and revised by the authors for this presentation. We trust that by collecting these reviews in a single publication we have provided a service to research scientists, teachers, and students in cardiovascular physiology.

This book will be available in the spring of 1982. It contains 312 pages and 94 figures. The list price is $33.50, but the book may be purchased by APS members for $27.00 when they order directly from the Society headquarters, 9650 Rockville Pike, Bethesda, MD 20814.

Future Meetings

1982	
APS Fall Meeting	Oct 10-15, San Diego
1983	
FASEB Annual Meeting	Apr 10-15, Chicago
APS "Fall" Meeting	Aug 20-24, Honolulu
IUPS Congress	Aug 28-Sep 13, Sydney
1984	
FASEB Annual Meeting	Apr 1-6, St. Louis
*APS "Fall" Meeting	Jul 29-Aug 7, Lexington
1985	
FASEB Annual meeting	Apr 21-26, Anaheim
*APS "Fall" Meeting	Aug 4-9, Buffalo

*Campus meeting

APS Sections

Cell and General Physiology Section

Organization and Election of Officers

The Cell and General Physiology Section of the American Physiological Society was officially organized at the FASEB meeting held during April 1981 in Atlanta. At this meeting nominations for officers were made, and subsequently the following officers were elected by mail ballot: Nick Sperelakis, Chairperson (one year); Mortimer M. Civan, Member of Council (two years); Margaret C. Neville, Member of Council (three years); Caroline S. Pace, Secretary/Treasurer (two years); Robert B. Gunn, Program Representative (three years).

As indicated, the council chose Nick Sperelakis as Chairperson for 1981–1982. Mortimer Civan will serve as Chairperson during 1982–1983, and Peggy Neville will be Chairperson during 1983–1984.

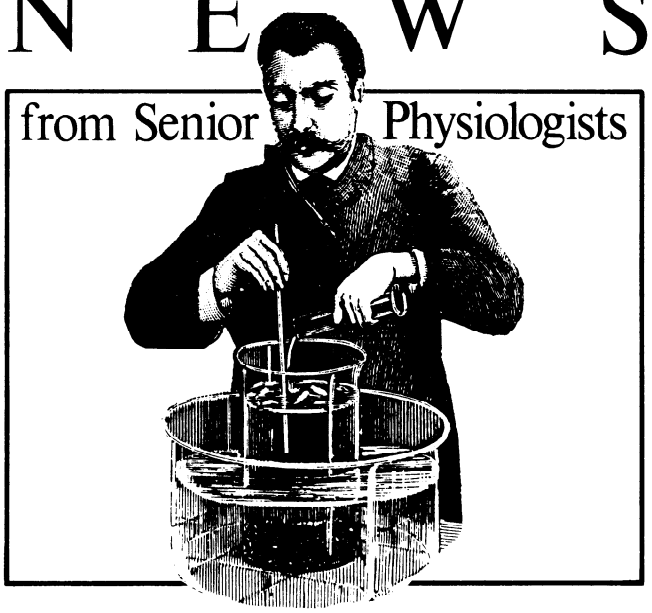
FASEB Meeting 1982

Dr. George Sachs will be guest speaker for the Cell and General Physiology banquet to be held Wednesday, April 21, at the FASEB meetings in New Orleans. The title of the lecture is "Proton Translocating Mechanisms in Cells and Organelles." The banquet will be held in the New Orleans Hilton, and tickets will be sold in the registration area.

FASEB Meeting 1983

The Steering Committee of APS–Cell have decided to develop the theme of communication within and between cells for future meetings. Tentative topics for symposia to be held in Chicago, April 10–15, 1983, are "Electrophysiology of Secretory Cells," "Cell-to-Cell Communication," and "Role of Calcium as Second Messenger."

NEWS from Senior Physiologists



Stanley Bennett to Hallowell Davis:

I became Professor Emeritus at the University of North Carolina at Chapel Hill in July 1981. I stepped down from administrative responsibilities as Chairman of Anatomy about four years ago and gave up most of my teaching about two years ago. Since then, I have had a good deal of time for research and have been able to reinvigorate my experimental and theoretical research work. By special arrangements with the Dean, I am permitted to continue working in my laboratory and office. These are located in a trailer and are very satisfactory. I have good administrative support from the Department, free use of the library, and am eligible to apply for research grants, though my needs for research funds are rather modest.

My research work at present is directed toward better understanding of the general role of actin and myosin in cells and toward improvement in our knowledge of the structural basis for electrical synaptic communication between cells. I continue my editorial duties for several journals and my national and international activities in science. I continue to receive invitations to write reviews, to give lectures, and to participate in and to organize symposia. I propose to keep busy in research as long as I can be productive. I am very grateful for the provisions that the University of North Carolina has made to permit me to continue my research and my participation in the intellectual life of the University.

Amongst my avocations, I have had to give up mountain climbing. I continue to do most of the physical labor on my 47-acre place just outside of Chapel Hill, where I have started a personal arboretum with about 200 varieties of trees, a number of which are, as far as I know, not represented in other collections in eastern North America. I have the impression that my efforts in experimental sylviculture are creating one of the better collections on the east coast. In this work, as in my laboratory work, I do almost everything else myself. I have neither technicians nor students with me. I carry out my research much as I did when I was a postdoc at Harvard, more than 40 years ago. At that time I cherished my many contacts with you and with my other friends in the physiology department. Recently I visited Bob Morison in Petersboro and found him vigorous and in good spirits.

Best wishes to you and to my other friends on the committee.

Dept. of Anatomy
University of North Carolina
Chapel Hill, NC 27514

Ernest A. Spiegel to Hal:

Thank you very kindly for your and the American Physiological Society's good wishes to my 86th birthday. My latest monograph on "Guided Brain Operations" is in press (Karger, Basle). It shows the worldwide acceptance of the stereotactic method originally used by Horsley and Clarke in cats and monkeys and applied by me to the human brain. A major part of the book is devoted to the contributions to the physiology of subcortical structures in man. Recently I was invited by the World Society for Stereotactic and Functional Neurosurgery to address their Zurich meeting by trans-Atlantic telephone. I discussed the function of the ganglion psalterii (subfornical organ), a cell group which I discovered and which is demonstrable in all mammals including man, the pathophysiological mechanism of pain relief by stimulation of the posterior columns, and the role of endogenous peptides in the functioning of some subcortical structures.

6807 Lawton Ave.
Philadelphia, PA 19126

Helge E. Ederstrom to Edward Adolph:

Since retiring at 70 of age in 1978, I have kept active in several pursuits. I maintain a matchbox-size office at the University of North Dakota Medical School and keep in contact with the events in the Dept. of Physiology. Much data lies in my files awaiting publication, but I doubt that it will appear in print. However, one of my graudate students and I published in a recent *Journal of Applied Physiology.*

Another pursuit of mine has been a historical report of the School of Medicine here, with emphasis on the teaching of physiology and pharmacology. This will be included in the 100th anniversary compendium of history of the University in 1983. It has been most interesting to pursue old college catalogs and read the list of former teachers and the subjects taught in the beginning years of the medical school in 1905. Further information and anecdotes are coming in from old graduates who have been contacted.

Now that my academic duties have shrunk, I have had more time to spend on my lifelong hobby of water-color painting. Last fall I had a one-man show of some 40 paintings at the University Art Gallery. The exhibit contained mostly realistic North Dakota rural scenes—abandoned farm buildings, old machinery, and my favorite subject, grain elevators. Most of the paintings were sold. Also, I have had smaller exhibits around the area.

My teaching has taken a complete turnaround, in that I now teach a course in painting each semester at the University Art Center. Both college students and townspeople are enrolled, and it has proven quite a novel challenge to a scientist.

The Physiologist is a most welcome journal in my retirement years, since it is a main contact with old friends and colleagues. I would like to suggest that at one of the fall meetings there should be scheduled a dinner or cocktail party for senior physiologists, where we could reminisce about events of the past years and renew old friendships.

Thank you for your efforts in behalf of us retirees and old-timers.

Dept. of Physiology
University of North Dakota School of Medicine
Grand Forks, ND 58202

Samuel Matthews to Edward:

It is indeed a long time since we attended meetings together or enjoyed summers at Woods Hole.

I retired in 1970 but continue to make my home in Williamstown and have maintained fairly close contacts with the college. For a number of years after retirement I served as a consultant and editor for a publishing house. This activity ended several years ago, and now my chief contact with the sciences is by means of the fairly numerous seminars and lectures by staff members and invited guests at the college. I find these stimulating and a painless method of keeping abreast with what is happening in the sciences.

Just before retirement we visited a former student who was working on the natural history of the manatee in Crystal River, Florida. We liked the small town at the head of the river so much that we took an apartment on the river for several of the winter months for a number of years. Increasing crowds in Florida and increasing years have lessened the attractiveness of the change, so beginning last year we stayed in Williamstown and found we actually enjoyed the Berkshire winter.

As you may know Williamstown developed at the crossing of two old Indian trails, one from East to West, one from South to North. Two major highways developed more or less along these trails with the result that Williamstown, as someone has put it, is a convenient place to go through. One pleasant result of this is the number of old friends and former students that do go through but find the time to stop and renew old acquaintances.

I have no "words of wisdom" to pass along to younger colleagues. Retirement objectives must be almost as individualistic as fingerprints, and in any case I fear advice from age to youth is usually received with the indifference, amusement, or contempt that it usually deserves. I only wish all of them well.

Dept. of Biology
Williams College
Williamstown, MA 01267

Alberto Hurtado to Edward:

Thanks very much for your cordial greetings. I feel fine and am still working on a monograph on altitude. I do not forget the pleasant and useful years I spent in Rochester. With best regards and personal greetings.

Universidad Cayetano Heredia
Apartado 5045
Lima, Peru

John A. Zapp to Horace Davenport:

Thank you for your inquiry about my current activities. I retired from full-time employment at age 65 in 1976, at which time I had been Director of DuPont's Haskell Laboratory for Toxicology and Industrial Medicine for 24 years. Since that time I have been an individual consultant (no employees) to a number of large corporations, on a part time and selective basis and have enjoyed this activity very much.

I have continued with some scientific writing since retirement, the latest being a chapter ("Industrial Toxicology—Retrospect and Prospect") in Patty's *Industrial Hygiene and Toxicology* (3rd ed.), Wiley Interscience, 1981 (vol. IIa). The words of wisdom which I might pass on to younger colleagues would be contained in a 1977 article. They are, in summary, don't let your emotions interfere with your exercise of the scientific method.

316 Marshall St.
Kennet Square, PA 19348

Hugh Montgomery to Horace:

Thank you for your invitation to send my news items for *The Physiologist* and for your personal remarks about some of our early work on pH in plasma, glomeruli, and various parts of the tubules. What a long time ago that was! My only earlier work was on the hemocyanins in the bloods of various sea animals—first paper 1928. Since then my physiological work has mainly concerned oxygen delivery to the skin of man. I think that in 1940 we may have been the first to show the wide range and very rapid changes in the P_{O_2} in even the relatively slowly metabolizing tissue. I remember that it interested Gene Landis, with whom I had previously worked in about 1938.

Since 1960 my work has been mainly clinical, growing from investigations in the peripheral vascular field, first centered at the Hospital of the University of Pennsylvania and later at the Bryn Mawr Hospital. I have lived to see the medical specialty that was called peripheral vascular disease dwindle and be largely absorbed by the surgeons. This may be a good temporary development, but the field must eventually revert to medicine to regain its proper development.

Two years ago, at age 75, I retired from even the clinical work and am now most happily absorbed in many unimportant things that I never previously had sufficient time to do well and so to enjoy. I like to think these things can be summarized as being the activities of an amateur naturalist.

932 Merion Square Rd.
Gladwyne, PA 19035

Correction

The first Managing Editor of Physiological Reviews was Donald R. Hooker and not Davenport Hooker as listed in *Physiology, 1850–1923: The View from Michigan,* a Supplement to *The Physiologist* 25(1): 76, 1982.

SYMPOSIUM ON BLOOD OXYGEN AFFINITY AS A FACTOR IN TISSUE OXYGEN DELIVERY

Held at the Fall Meeting of APS in Cincinnati; October, 1981

Stephen M. Cain

Department of Physiology and Biophysics
University of Alabama in Birmingham

INTRODUCTION

The affinity of hemoglobin for oxygen is a physiologic variable. It can be manipulated by man and by nature to change the ease with which oxygen is loaded at the lung and discharged at the tissues. Changes in blood oxygen affinity take place in every capillary which participates in gas exchange as blood performs its gas transport functions. There are reciprocal changes in hemoglobin affinity for oxygen and for carbon dioxide and hydrogen ions at capillaries as red cells carry these ligands of hemoglobin between lung and tissue. This is a model system that satisfies most of the criteria for a facilitated transport mechanism.

In addition to the changes in blood oxygen affinity as blood makes its circuit through the body, a wholesale shift of the position of the oxyhemoglobin dissociation curve can take place with such events as acidemia, alkalemia, and changes in another hemoglobin ligand, 2,3-diphosphoglycerate. The discovery of the functional role played by 2,3-DPG during the mid-60's sparked volumes of research. Changes in DPG concentrations were measured in response to all sorts of conditions. The direction of change found in many of the conditions that were studied indicated that natural alterations in DPG levels generally acted to maintain tissue PO_2.

The importance of changes in dissociation curve position is in the possible effects on tissue oxygenation. A leftward-shifted curve has a P_{50} lower than normal and releases oxygen less readily; in other words, at a lower PO_2. A rightward-shifted curve, on the other hand, has a higher than normal P_{50} and releases oxygen at a higher PO_2. At a lung capillary, a rightward-shifted curve would load normally at usual sea level alveolar PO_2 and would release oxygen at a higher than usual PO_2 in the tissue capillary. These events would occur only if no physiologic compensation occurred to preserve tissue PO_2. Furthermore, if alveolar PO_2 is lower than normal, a right-shifted curve may not be able to load O_2 to near saturation of hemoglobin as usually occurs. This has given rise to the idea of a crossover point where right vs. left shifted curves lose any advantage with respect to tissue oxygen transport.

The participants were asked to address the consequences of changes in blood oxygen affinity upon the state of tissue oxygenation. For example, does a left-shifted curve actually lower tissue PO_2 or do compensatory responses at the tissue level prevent or buffer such a change? That leads to more fundamental questions of whether tissue PO_2 is regulated and, if so, what serves as the sensor at the tissue level. What is the magnitude of the diffusion barrier at the tissue level? Will an increase in mean capillary PO_2 deliver more oxygen in a situation where tissues are not meeting their oxygen demand or will an increased total transport at the same capillary PO_2 work better? In other words, do the adjustments of microcirculatory perfusion shorten effective intercapillary distances to the point that even small driving pressures are sufficient to deliver the available oxygen to the tissue? Will so-called affinity hypoxia evoke preferential distribution at the organ system level like other forms of hypoxia so that heart and brain oxygenation is favored?

Some of these questions were answered in the presentations but still more arose in a lively discussion between the audience and the participants which was moderated by C. Lenfant of the Fogarty International Center, NIH. All were agreed that a major difficulty opposing ready answers to questions of tissue oxygen delivery is the assessment of tissue oxygenation relative to need and function. A universally useful approach to this difficulty remains as a challenge to all who are involved in this area of research.

SOME IMPLICATIONS OF BLOOD OXYGEN AFFINITY FOR FETAL GROWTH AND TRANSITION TO EXTRAUTERINE LIFE

J. Metcalfe
University of Oregon

In many species that have been studied, the blood oxygen dissociation curve of the fetus or embryo lies to the left of that characteristic of adults of the same species. The high oxygen affinity of fetal blood seems well suited for improved oxygen uptake and release at the low oxygen tensions characteristic of the fetal environment.

Experiments designed to test the importance of low fetal blood P_{50} have yielded conflicting results. Several groups of investigators have performed exchange transfusions of chronically catheterized sheep fetuses, displacing their

blood oxygen dissociation curve so that it became identical with that of adult blood. Only one group has observed a drop in fetal oxygen consumption and the appearance of fetal acidosis following the exchange transfusion and these undesirable effects appeared to depend upon a halving of umbilical blood flow. Other investigators have observed no change in fetal oxygen consumption following an apparently identical protocol.

When the difference between the oxygen affinities of maternal and fetal blood is reduced by increasing the oxygen affinity of maternal blood in pregnant rats, fetal growth is jeopardized. This conclusion has been established by two independent groups of investigators, and one documented an apparently compensatory hyperplasia of the placenta.

In most mammals that have been studied, blood oxygen affinity falls shortly after birth. Because the mechanisms regulating blood oxygen affinity vary in different species, the mechanism responsible for the fall in affinity after birth varies widely. In dogs, the decline is due to a rise in 2,3-DPG, secondary to a fall in pyruvate kinase activity. In sheep, the postnatal decline in blood oxygen affinity appears to depend upon a rise in blood glucose level.

In summary, the relatively high oxygen affinity of fetal blood appears to be an adaptation to the relatively low oxygen tension in the fetal environment. Following the onset of air breathing with birth, blood oxygen affinity declines, one of a series of adaptations that the newborn individual makes in adapting to its new environment.

THE EFFECT OF THE O_2 DISSOCIATION CURVE ON THE EFFICIENCY OF O_2 DELIVERY IN BLOOD

Z. Turek and F. Kreuzer
University of Nijmegen, The Netherlands

A change of blood O_2 affinity, i.e., a shift of the blood O_2 dissocation curve (ODC) can affect the efficiency of the O_2 transport in blood from the lung capillaries to tissues.

Under hypoxic hypoxia both theoretical studies (Physiologist 23: 25, 1980) and experiments in rats with a normal and a left-shifted ODC have shown that a decrease of blood O_2 affinity, a shift to the right, improved the efficiency of O_2 transport in blood at mild hypoxia but impairs it at deep hypoxia. A shift to the left has an opposite effect, it decreases the efficiency of O_2 transport during mild hypoxia but increases it substantially during severe hypoxia.

These conclusions do not apply to other types of hypoxia, in particular not to the case where arterial PO_2 is low because of ventilation-perfusion inhomogeneities in the lung (shunt effect), while breathing air at sea level. Under such circumstances a shift of the ODC to the right is expected to be beneficial even at very low arterial PO_2.

EFFECTS OF ACID AND BASE INFUSIONS ON O_2 TRANSPORT DURING HYPOXIC, ANEMIC, AND STAGNANT HYPOXIA

S.M. Cain and R.P. Adams
University of Alabama in Birmingham

In order to observe the effect of altered hemoglobin O_2 affinity upon oxygen delivery, pH was increased or decreased while anesthetized and paralyzed dogs were made hypoxic either by breathing a low O_2 gas mixture, by exchanging blood for 6% dextran, or by decreasing cardiac output. In the first set of experiments using hypoxic hypoxia, a hyperventilated group was also infused with bicarbonate so that pH was 7.54 during hypoxia. The acid group was ventilated with 9.3% O_2 plus 7.1% CO_2 so that pH fell to 6.99. In all cases, O_2 uptake was decreased during hypoxia by the supply limitation. The acid group had greater O_2 availability at the lung during hypoxia and significantly higher levels of arterial and mixed venous PO_2 than the alkalotic group. In spite of that, survival time in hypoxia was not different. Both groups fell on a common line ($r=0.89$) relating O_2 uptake to total O_2 transport (cardiac output x arterial O_2 content) whereas there was no correlation of O_2 uptake and either arterial or mixed venous PO_2. The tissues appeared to extract O_2 just as efficiently from alkaline blood as from acid blood of lower O_2 affinity.

In the case of anemic hypoxia, the total O_2 transport was again too little to support O_2 uptake at the normocythemic control level. Alkaline infusion transiently raised O_2 uptake whereas acid infusion decreased it. This was due to a temporary increase in cardiac output with infusion of bicarbonate. When O_2 uptake was again examined in relation to total O_2 transport, acid infusion acted to increase the extraction of O_2 by peripheral tissues. This may have been the result of acid stimulating adrenal medullary secretion. If this action increased peripheral vasoconstrictor tone, then blood flow may not have overperfused areas of low O_2 demand to create the equivalent of peripheral shunting. Since anemia does not stimulate carotid chemoreceptors, vasoconstriction of peripheral vascular beds may not have been as effective in anemic as in hypoxic hypoxia.

In a third set of experiments, stagnant hypoxia was induced by two means: cardiac tamponade and hemorrhage. The decreased hemoglobin affinity for O_2 caused by acid infusion increased calculated values of tissue capillary PO_2. In these experiments, O_2 transport and uptake in the intact left hindlimb (less paw) were compared to those events in the whole body. Limb O_2 uptake increased during the periods of stagnant hypoxia while whole body O_2 uptake was significantly decreased. Before acid or base infusion, the slopes of the lines relating total O_2 transport and O_2 uptake were the same for both shock models. Acid increased the slope of the whole

body line in both groups but base infusion did not change it. In the limb, base infusion decreased the slope of the line in the hemorrhage group whereas acid infusion did not alter the slope of either group. These results indicated that, in the whole body, acid improved the matching of blood flow to tissue O_2 demand at the organ system level. In the limb, effective intercapillary distances may have been increased by loss of blood volume in the hemorrhagic shock model. In this instance, a tissue capillary PO_2 that was elevated by a decrease in hemoglobin O_2 affinity may have aided diffusion across these greater distances and improved tissue O_2 delivery during hemorrhagic shock. In the three forms of tissue hypoxia, acidemia or a rightward shifted dissocation curve or both do seem to improve effectiveness of O_2 transport when O_2 uptake has become transport limited.

OXYGEN DISSOCIATION CURVE SHIFTS: EFFECTS IN EXPERIMENTAL MODELS

R.D. Woodson
University of Wisconsin

Several investigators have considered the effects of shifts of the oxygen dissociation curve (ODC) on tissue oxygen delivery in animal models. When leftward shifts are produced in otherwise normal animals, no changes in cardiac output, heart rate, respiratory rate, arterial blood gases and oxygen consumption occur. We have recently found, however, that major increases in coronary and cerebral flow occur in normal rats when the ODC is shifted to the left by exchange transfusion of blood containing carbamylated or DPG-depleted red cells. Analysis suggests that these flow changes are required to maintain oxygen flux in these organs in the face of the ODC shifts.

The role of the ODC in tissue oxygen delivery is further delineated by experiments in which left shifts of the ODC are produced in animals lacking the ability to respond with flow compensation. When a leftward ODC shift produced by exchange transfusion is combined with hypovolemic shock, animals tolerate shock significantly less well than controls exchange tranfused with normal blood, both in terms of behavior during shock and post-shock survival. We have also examined the effect of blood with a left-shifted ODC in the isolated dog brain. When perfused with control blood at a flow rate normal for the dog, EEG and oxygen consumption are normal. When blood with a 12 Torr left shift is substituted, the EEG deteriorates significantly and cerebral consumption drops by 25%. Valeri and colleagues have shown analogous changes in hypothermic canine myocardium. Panteley et al. have shown the converse effects in a canine myocardial infarction model, namely a reduction in amount of infarcted tissue when the ODC was shifted to the right.

We thus conclude that the heart and brain are relatively vulnerable to decreases in oxygen supply in the range produced by a shift of the ODC. When this occurs in normal animals or subjects, flow compensation is likely to offset the effect. When this adaptive response is blunted, as in vascular disease or shock, a left shift produces tissue hypoxia.

RELATIVE SIGNIFANCE OF HbO_2 DISSOCIATION CURVE SHIFTS, IN EXERCISE AND IN CHRONIC HYPOXIA

J.A. Dempsey
University of Wisconsin

Strenuous physical exercise induces substantial rightward shifts in the HbO_2 dissociation curve; i.e., during prolonged heavy work with the legs, P_{50} in femoral venous blood increases 12 to 16 mmHG secondary to metabolic and respiratory acidosis (P_VCO_2 > 60 mmHg, pH_V < 7.22) and increased vascular temperature (T_V > 41°C). The relevant question here is, does this shift really protect against an otherwise insufficient diffusion gradient for O_2 from muscle capillary to mitochondria? In examining this question in a variety of exercise conditions in normoxia and hypoxia, one must consider: a) the net effect of this shift on in vivo capillary PO_2, whereby a rightward shift in arterial blood will lower CaO_2 and the extent to which this is counterbalanced in femoral venous blood will depend upon the position of this end-capillary blood on the steep or flatter (converging) portion of the curve; and b) the level of the so-called "critical" capillary PO_2 which must be protected to ensure adequate diffusion.

In heavy work at sea level or even moderately high altitude (< 3500 m) a rightward shift clearly spares PO_2 along most of the working muscle capilalry (+3 to 5 mmHg PO_2 at end-capillary), because arterial PO_2 remains high so that a rightward shift causes < 1 vols % O_2 content to be "lost". Since a-v O_2 content difference is not maximal, the rightward curve shift in femoral venous blood does not occur on the lower, (converging) portion of the curve. With exercise at higher altitudes, however, the rightward shift in the curve produces negative effects on PO_2 along the latter portion of the capillary because: (1) arterial PO_2 falls (with exercise) to the steeper portion of the curve and thus causes the rightward shift to result in substantial loss of O_2 content; and (2) the a-v (femoral) O_2 content widens to near maximum and thus the curve shift is not reflected to any significant extent (< 1 to 2 mmHg) in end-capillary blood. The exaggerated a-v O_2 difference at high altitudes results because of the exercise-induced arterial desaturation and because cardiac stroke volume and output are decreased (below sea-level values) at a given exercise $\dot{V}O_2$. Similar condition exist at sea level in the highly trained athlete capable of achieving very high maximal metabolic rates and who shows significant exercise-induced arterial hypoxemia (-20 to -35 mmHg PaO_2 decrease from resting values). Further, it was shown that a gradually falling P_VO_2 during prolonged (constant load) work at sea level and high

altitude produced no discernible efflux of lactic acid from the contracting muscle(s) until end-capillary PO_2 was < 5-7 mmHg; i.e. diffusion gradients for PO_2 were apparently "adequate" for "aerobic" metabolism at or above these very low values for $P_{\bar{v}}O_2$.

We conclude that exercise-induced rightward shifts in P_{50} may have either very small or even negative net influences on capillary PO_2 in skeletal muscle; depending upon the degree to which PaO_2 is maintained and the extent to which the $\dot{V}O_2$ content difference is widened across the working muscle. Perfusion of the exercising muscle (> 85% of total $\dot{Q}$) is the clearly dominant factor determining intercapillary and thus diffusion distance; to such an extent that capillary PO_2 (or diffusion gradient) becomes a relatively monor consideration in ensuring adequate tissue oxygenation.

USE OF LOW AFFINITY RED CELLS IN THE TREATMENT OF ANEMIC HYPOXIC PATIENTS WITH NORMAL OR REDUCED ARTERIAL OXYGEN TENSIONS AT NORMOTHERMIC OR HYPOTHERMIC TEMPERATURES

C.R. Valeri
Boston University

Although serious efforts to improve the oxygen transport function of preserved red blood cells are relatively recent, the knowledge that liquid-stored red blood cells suffer an impairment of this function is not new. Valtis and Kennedy in 1953 reported a respiratory defect occurring during the first week of storage of red blood cells in the ACD anticoagulant, and demonstrated that this defect was corrected *in vivo*, usually within 24 hours after transfusion. In 1967 Benesch and Benesch and Chanutin and Curnish reported that this respiratory defect in red blood cells was caused by deterioration of red blood cell 2,3 DPG during blood storage at 4°C.

A reduction in a patient's red blood cell volume of about 40% usually is compensated for by an increase in the 2,3 DPG level from 0.8 M DPG per M Hb to 1.6 M DPG per M Hb, which is two times the normal level. This compensatory *in vivo* increase in 2,3 DPG obviates the need for an increase in cardiac output to ensure an adequate supply of oxygen to tissue and to maintain high tissue oxygen tension. Our observations of the role of red cell 2,3 DPG in maintaining optimum oxygen transport function stimulated us to treat red blood cells with a rejuvenation cocktail to restore or increase 2,3 DPG and ATP levels. The approach is to incubate red blood cells in a solution composed of pyruvate, inosine, phosphate and adenine (PIPA Solution), for 1 hour at 37°C. Human red blood cells with elevated 2,3 DPG levels have been transfused successfully to normothermic patients with severe pulmonary insufficiency.

Patients undergoing cardiopulmonary bypass surgery for abdominal aneurysm surgery with hypothermia have been given red blood cells with two to three times normal 2,3 DPG and 1-1/2 times normal ATP with satisfactory results. During hypothermia, oxygen consumption decreases as a result of a decreased need for oxygen, ineffective utilization of oxygen by the tissue, or an increase in red blood cell oxygen affinity. This increased affinity for oxygen can be attenuated if the red blood cells administered during hypothermia have increased 2,3 DPG levels.

In patients in whom autoregulation of cerebral and coronary blood flow is not possible and in patients in hemorrhagic shock, the oxygen transport function of the transfused red blood cells is critical, and red blood cells with normal or increased 2,3 DPG levels would ensure oxygen availability to the brain and heart. In these patients, red blood cells with low 2,3 DPG may prove harmful

Questions have been raised as to whether there might be situation in which 2,3 DPG-enriched red blood cells might be contraindicated, for instance, whether the decreased affinity for oxygen associated with the transfusion of red blood cells with two to three times normal 2,3 DPG levels might impair oxygenation of the red blood cells in the lungs. Red blood cells with two to three times normal 2,3 DPG are not recommended for patients in whom arterial PO_2 tension is less than 40 mmHg.

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. 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 correct 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 5 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.
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Membership Secretary
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SPECIAL INFORMATION AND INSTRUCTIONS

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Bylaws of the Society:

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

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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. Orally present or co-author a contributed paper and sponsor a non-member authored paper at the Fall scientific meeting.
7. Orally present or co-author one contributed scientific paper at the annual Federation meeting or sponsor one paper.
8. Receive The Physiologist.
9. Receive Federation Proceedings, Public Affairs Newsletters and annual Membership Directory.
10. Subscribe to handbooks and periodicals published by the Society at membership rates.
11. Register to attend scientific meetings of the Federation and the APS Fall meeting at membership rates.
12. 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).
13. Eligible to receive the Daggs Award.
14. Eligible to be selected as Bowditch Lecturer (members under 40 years of age).

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3. Sponsoring New Members.
4. Receiving the Daggs Award.
5. Selection as Bowditch Lecturer.

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

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Duties and Privileges:

1. Present one contributed paper at 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.
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Submit original and 7 copies of application and supporting documents.

APPLICANT'S LAST NAME _____

Date _____

THE AMERICAN PHYSIOLOGICAL SOCIETY
9650 Rockville Pike, Bethesda, MD 20014

MEMBERSHIP APPLICATION FOR:

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1. EDUCATIONAL HISTORY

Dates	Degree	Institution	Major Field	Advisor

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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
_____	☐	☐	_____	☐	☐
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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.

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Salt and Water Absorption in the Proximal Tubule

JAMES A. SCHAFER
Nephrology Research and Training Center
Departments of Physiology and Biophysics, and Medicine
University of Alabama in Birmingham
Birmingham, Alabama 35294

The operation of most vertebrate kidneys depends on the ultrafiltration of a large volume of fluid compared with the final urine volume. In the mammal, this high rate of glomerular ultrafiltration is responsible for the clearance of nitrogenous wastes with only very limited involvement of tubular absorptive and secretory processes for these solutes. However, the high rate of glomerular filtration also necessitates a correspondingly high rate of tubular salt and water absorption most of which is accomplished by the proximal nephron. In the human, the proximal convoluted and straight tubules continually absorb in excess of 80 ml of fluid each minute. This rate of fluid transport, when considered on the basis of the total surface area of the proximal tubules, is greater than occurs across any other epithelial cell layer in the body.

In reviewing this topic, I would first like to consider solute transport in the proximal tubule in terms of the quantities that are absorbed as well as the mechanisms by which the absorption of different solutes may be coupled. Second, I will try to develop those concepts on which our present hypotheses concerning the coupling of solute absorption to volume absorption are based. Finally, I will briefly discuss the final event in the absorptive process, i.e., the return of the absorbed solute and water to the blood via the peritubular capillary circulation. Unfortunately, the latter process has been the most difficult to study quantitatively, and yet it may be the most important event which is modulated when the rate of solute and water absorption in the proximal tubule is altered.

Tutorial lecture, 32nd Annual Meeting of the American Physiological Society, 14 October 1981, in Cincinnati, OH.

Solute Absorption in the Proximal Nephron

As a basis for comparison, consider the total quantity of solute absorbed per minute by the proximal tubules. For illustration I have chosen the rate, because the most complete data on in vivo rates of glomerular filtration and proximal volume absorption are available from micropuncture studies in this animal. For an average glomerular filtration rate (GFR) in the rat of approximately 2.3 ml/min (5, 23) and an ultrafiltrate osmolality of 290 mosmol/l, one can calculate that the filtered solute load is approximately 670 μosmol/min. Of this total amount, at least 60% is absorbed in the proximal convoluted tubule (13, 34), i.e., about *400 μosmol/min.* I will recall this particular amount of total solute absorption for comparison to the absorbed quantities of individual solutes as discussed below.

Of course, most of the absorbed solute in the proximal tubule consists of the same electrolytes present in abundance in the plasma, i.e., sodium, chloride, and bicarbonate, as shown in Table 1. The ratio of chloride to bicarbonate absorption is less than the ratio of their concentrations in plasma, because bicarbonate is preferentially absorbed in the proximal tubule (14). The preferential absorption of solutes such as bicarbonate is an important issue that I will return to later. The absorption of organic anions, sulfate, and phosphate also contributes to the absorbed osmols. In total, these electrolytes account for about 370 μosmol/min of the 400 total absorbed in the proximal convoluted tubule.

It has been established that the active transport of sodium across the proximal tubule epithelium is due to the operation of the Na^+-K^+-ATPase, which is located in the basolateral (or peritubular) membranes of the proximal tubule cells, and I will refer to this enzyme as the sodium pump. However, as illustrated in Fig. 1, for sodium to be absorbed across the proximal tubule epithelium, sodium ions must gain access to the pump site.

Table 1

Quantities of Primary Electrolytes Absorbed by Rat Proximal Convoluted Tubule

Electrolyte	μosmol/min
Na^+	185
K^+	5
Cl^-	125
HCO_3^-	45
Organic anions and sulfate and phosphate	20
Total	370

Rates of electrolyte absorption are approximated here from concentrations of the electrolytes in plasma ultrafiltrate (1, 18, 24), a GFR of 2.3 ml/min (5, 23) and fractional absorptions of 60% for Na^+ and K^+ (12), 90% for HCO_3^-, and 50% for Cl^- (12, 14). Total absorption of the other anions is calculated assuming from requirements of electroneutrality.

One potential mechanism for access to the pump site is via a conductive diffusional pathway across the luminal cell membrane (Fig. 1*A*). Of course, in addition, there are also conductive pathways for sodium movement through the junctional complexes between adjacent proximal tubule cells. The latter pathways could also permit a fraction of the Na^+ absorption to be coupled to the absorption of water by solvent drag. More recently we have become aware that sodium may also gain access to the tubular cell across the luminal membrane by mechanisms involving cotransport of the sodium ion with other solutes such as sugars and amino acids or with anions such as lactate, chloride, phosphate, or citrate (Fig. 1*B*). Evidence for the presence of cotransport mechanisms has come primarily from transport studies in isolated luminal (brush border) membranes in numerous laboratories (for references see 20, 26, 36). Of course these mechanisms have received considerable attention because the cotransport of sodium ions downhill into the cell can be used to provide the energy required for the active transport of the organic solutes or anions across the epithelium. However, it is also important to consider the fact that these organic solutes and anions also serve a permissive role in providing a route for sodium entry into the cell and access to the sodium pump. In the absence of the organic solutes such as amino acids and sugars, access to the pump site is diminished and sodium absorption is correspondingly diminished, which is a point that I will return to below. Finally, sodium entry into the cell across the luminal membrane can also occur by countertransport of protons out of the cell into the lumen (Fig. 1*C*). This antiport mechanism has been demonstrated by Murer and his collaborators (19) and has been confirmed in other laboratories. The mechanism would provide a means of proton secretion as well as sodium absorption. These three mechanisms shown in Fig. 1 (conductive entry, cotransport, and Na^+-H^+ antiport) are not intended to represent alternative hypotheses, but rather there is every indication that all three processes occur simultaneously and are involved to varying extents in the transport of sodium.

Obviously the transepithelial movement of sodium ions must also be accompanied by an equal flux of anions the bulk of which is chloride. Figure 2 depicts the mechanisms by which chloride has been proposed to cross the epithelium. Under conditions where the chloride concentration is slightly elevated in the lumen and/or there may be a lumen-negative voltage, chloride can move passively down its electrochemical potential gradient from the lumen to the peritubular space by diffusion (and possibly also solvent drag, see Ref. 3) through conductance pathways either in junctional complexes between the cells or in the luminal and basolateral membranes (Fig. 2*A*). More recently an additional mode of chloride transport has been identified in the luminal membranes of several types of epithelia. This process involves an electroneutral cotransport of sodium and chloride ions (Fig. 2*B*). Chloride in the cell then moves down an electrochemical potential gradient to the peritubular solution presumably through conductive pathways in the basolateral membranes. It should, however, be noted that several studies have shown the chloride conductance of these membranes to be very low (see Ref. 33). And recently Shindo and Spring (33) have proposed that chloride may move across basolateral membranes by cotransport with sodium or potassium. In many types of epithelia, the coupled transport process at the luminal membrane is capable of producing an active transport of chloride from the luminal to the peritubular solution. However, in the case of leaky epithelia such as the gallbladder and the proximal tubule, it appears that the process is passive. An alternative mode of chloride entry has been proposed by Warnock and Yee (37). Using vesicle methodology, these investigators have confirmed the existence of conductive chloride channels in the luminal brush border

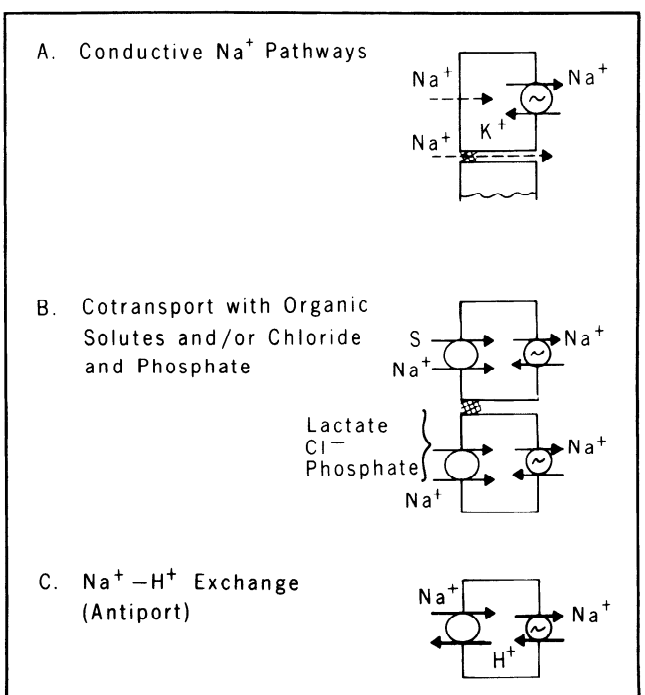

Figure 1.

Mechanisms by which Na^+ may cross luminal plasma membranes of proximal tubule during transepithelial absorption. Tubule lumen is on *left* of each diagram and peritubular space to *right*. Pump site is presumed to be Na^+-K^+-ATPase, which is localized to basolateral membrane. But transepithelial Na^+ transport depends on access of Na^+ to pump site by moving across luminal membrane via *A*, conductive pathways; *B*, cotransport; or *C*, antiport in exchange for H^+.

membranes as indicated in Fig. 1*A*, but in addition they have provided evidence for the existence of a chloride-hydroxyl exchange process in this membrane. This transporter would complement the sodium proton exchange process such that sodium chloride would move into the cell in exchange for protons and hydroxyl ions moving outward (Fig. 2*C*). However, the secretion of protons in exchange for sodium ions also results in bicarbonate absorption that would also accompany the transported sodium ions. In the early proximal tubule, bicarbonate absorption could be effectively coupled to the absorption of sodium by this antiport mechanism. However, as the luminal bicarbonate concentration falls in the later regions of the proximal tubule, Cl^--OH^- exchange would predominate. Thus although Na^+ and Cl^- absorption are coupled, this coupling is less rigid than a strict Na^+-Cl^- cotransport.

From the preceding discussion and Figs. 1 and 2, it can be seen that a large fraction of Na^+ absorbed by the proximal nephron may be accompanied by cotransported solutes. Table 2 provides an estimate of the amount of total solute absorption which involves the coupling of sodium entry at the luminal membrane with the entry of another solute. The primary cotransported solutes are bicarbonate (indirectly coupled), glucose, amino acids, phosphate, and organic anions. Table 2 gives the approximate percentage of each solute absorbed in the proximal *convoluted* tubule and the stoichiometry of the active absorptive process, i.e., the number of sodium ions transported for each molecule of solute. In the case of the amino acids, phosphate, and organic anions, the stoichiometry is variable and is estimated to be 1:1 on the average. On the basis of the filtered load of the solute and the percent absorbed, one may calculate in μosmol/min the total absorbed solute and the cotransported sodium ion. As you can see, if we compare the total absorbed osmols due to the active transported solute as well as sodium, it will make up at least 50% of the total 400 μosmol/min absorbed in the proximal convoluted tubule.

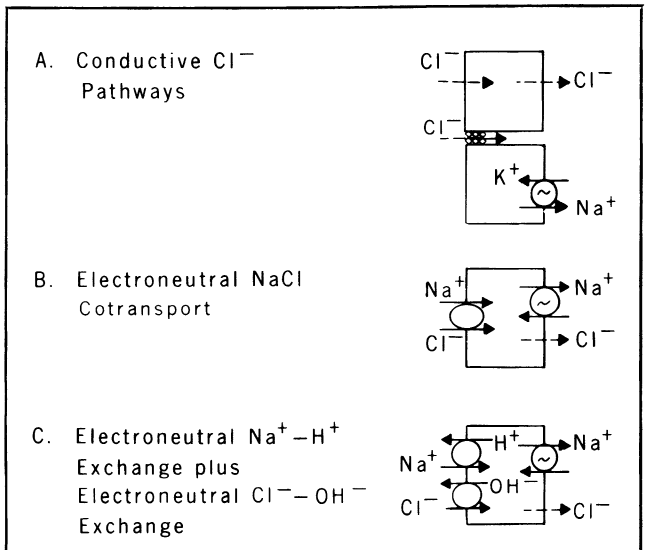

Figure 2.
Mechanisms of Cl^- absorption. Tubule lumen is on *left* of each diagram and peritubular space to *right*. *A*, Cl^- may move via conductive pathways across luminal and basolateral membranes and through electrically leaky junctional complexes. *B*, NaCl cotransport across luminal membrane with diffusional exit through a conductive pathway or an electroneutral coupled exit in basolateral membrane (see text). *C*, a combination of Na^+-H^+ and Cl^--OH^- antiport mechanisms in the luminal membrane.

Table 2
Absorption of Solutes Cotransported with Na^+

Solute	Absorbed, %	Stoichiometry Na^+/Solute	Absorbed Solute	Cotransported Na^+
				μosmol/min
HCO_3^-	90	1:1	45.5	45.5
Glucose	98	1:1	18.6	18.6
Amino acids	90	1:1 (avg)	6.2	6.2
Phosphate	50	1:1 (avg)	2.8	2.8
Organic anions	60	1:1 (avg)	27.8	27.8
Total			100.9	100.9
Grand Total			200 μosmol/min	

In summary, solute absorption in the proximal nephron involves the transport of about 400 μosmol/min in the rat convoluted segment alone. Over 90% of the absorbed solute load is due to sodium and potassium and the associated anions. There is preferential absorption of sugars, amino acids, organic acids, and bicarbonate driven by cotransport with sodium, and it is important to note that more than 50% of the sodium absorbed in the proximal convoluted tubule is coupled to the absorption of these actively transported solutes.

Volume Absorption by the Proximal Nephron

Volume absorption by the proximal nephron was demonstrated to be an example of isosmotic transport in the classical studies of Gottschalk and Mylle (15). These investigators obtained micropuncture samples of tubular fluid along the length of the proximal convoluted tubule of the rat. The osmolalities of these tubular fluid samples were measured and compared with that of the plasma to obtain a ratio of tubular fluid to plasma osmolality. In addition, urine was collected, and its osmolality was compared with that of the plasma. Several groups of animals were examined including those which had a very concentrated urine as a consequence of dietary water restriction and some which had diabetes insipidus with a resulting dilute urine. Nevertheless, in spite of the great variation in the osmolality of the final urine, Gottschalk and Mylle (15) found that the osmolality of the tubular fluid along the entire accessible length of the proximal convoluted tubule was indistinguishable from that of the plasma. It should be noted, however, that the reliability of such ultramicroosmolality measurements is only sufficient to determine that tubular fluid is within ±10 mosmol/l of the osmolality of systemic plasma. On the basis of these observations, the process of fluid transport in the proximal convoluted tubule was considered to be an example of what has been referred to as isotonic or isosmotic volume absorption. Because there was no apparent difference in the osmolality of the tubular fluid and the plasma, which would presumably be representative of the interstitial fluid, a mechanism had to be found that could explain the movement of fluid in the absence of an observable osmolality difference.

A general model for isosmotic volume absorption, often referred to as the standing gradient model, was developed by Diamond and Bossert (8) and was extended to the case of the proximal tubule with the additional recognition that solutes and water might past through junctional complexes at the luminal border (11). The basic postulate was that sodium is actively transported into the lateral intercellular spaces primarily at their closed ends. This active solute transport would produce a local hypertonicity in the space, and that hypertonicity could drive transcellular water flow. If the space were sufficiently long and the solute pumps were located near the closed ends (junctional complexes), then the model predicted that the fluid emerging from the basilar end of the lateral intercellular space could be isotonic to the cell contents. However, current information suggests that even though this model may be appropriate for many epithelia, it cannot operate to produce volume absorption in the proximal tubule. First, it has been shown that the Na^+-K^+-ATPase is localized not only at the closed ends of lateral intercellular spaces but all along the lateral and basilar membranes (17). Because of the high degree of infolding of the lateral membrane near the basilar end (38), the density of pump sites is probably much greater in this region than near the closed ends. Furthermore, because estimates of water permeability in most leaky epithelia suggested that large osmotic gradients would be required to produce the volume flow, this model was developed under the assumption that there had to be a relatively high osmolality in the lateral intercellular space in order to produce volume absorption. The production of hypertonicity in the lateral intercellular space also required that the space provide a sufficient restriction to the diffusion of solute. From transmission electronic micrographs it appeared that these lateral intercellular spaces were in fact long and tortuous and could provide a sufficient diffusion resistance. However, since the formulation of this model, it has been recognized that the lateral intercellular spaces offer very little diffusion resistance (28, 29, 38). Therefore, the intercellular spaces cannot be hyperosmotic with respect to the peritubular solution, at least in the proximal nephron. This means that the osmotic driving force for volume absorption must exist between external solutions, i.e., between the luminal and peritubular solution. This would appear to contradict the findings of Gottschalk and Mylle (15), who found no difference between tubular fluid and plasma osmolality. However, because the hydraulic conductivity of the proximal tubule has been shown to be extremely high, the required difference in osmolality between the lumen and the peritubular solution would be very small.

The osmotic water permeability in both the proximal convoluted tubule and the proximal straight tubule is in excess of 3,000 μm/s (2, 30). This permeability coefficient can be converted to the more readily appreciated units of hydraulic conductivity: each mosmol/l of osmolality difference would produce a net volume flow of about 0.25 $nl \cdot min^{-1} \cdot mm^{-1}$ of tubule length. Therefore, volume absorption in the proximal nephron, which may vary from 0.4 to 3.0 $nl \cdot min^{-1} \cdot mm^{-1}$, can be produced by an osmolality difference of only 1–10 mosmol/l. Alternatively, the hydraulic conductivity indicates that only about 0.01 $nl \cdot min^{-1} \cdot mm^{-1}$ of volume flow could be produced per mmHg of hydrostatic pressure difference between the lumen and peritubular solution. In other words, although the osmotic water permeability is high, the normally observed hydrostatic pressure difference between the proximal tubule lumen and the interstitial fluid would be insufficient to produce significant amounts of volume flow.

At this point it is interesting to go back to the explanation of isotonic fluid absorption that was given by Homer Smith in his classic book on renal physiology (35). "The simplest explanation is that as sodium and other constituents of the proximal tubular urine are reabsorbed, water diffuses back through the proximal tubule . . . to maintain an osmotic U/P ratio close to 1.0." If one reads between the lines a little bit here, it can be seen that Smith was implying that the proximal tubule had a high hydraulic conductivity such that only a small osmotic gradient would be sufficient to drive the water flow. This small osmotic gradient could then be developed by active solute transport from the lumen. If this were true, we might expect that as solutes are actively absorbed from the lumen, the tubular fluid would become slight hypotonic compared to the interstitial fluid. This hypothesis cannot be tested directly because the osmotic gradient may be too small to be detected. However, it can be demonstrated that rapid solute removal from the lumen is essential to the volume absorption process.

The dependence on active solute absorption has been demonstrated by experiments in which isolated rabbit proximal convoluted tubule segments were perfused with solutions of varying composition as summarized in Table 3 (7). When the perfusate resembled the glomerular ultrafiltrate and contained glucose, amino acids, and organic acids, the volume absorption was approximately 1.1 $nl \cdot min^{-1} \cdot mm^{-1}$. Removal of the preferentially absorbed solutes reduced the volume absorption, and in the absence of any of the above organic solutes in the perfusate, the volume absorption was less than half of that observed under control conditions.

The preferential absorption of organic solutes and bicarbonate occurs primarily in the early proximal convoluted tubule. In Fig. 3 the ratios of the tubular fluid to plasma ultrafiltrate concentration for several solutes are plotted as a function of distance along the proximal

Table 3

Effect of Organic Solute Removal on Volume Absorption in Isolated Perfused Rabbit Proximal Convoluted Tubule

Perfusate Composition	Volume Absorption $nl \cdot min^{-1} \cdot mm^{-1}$
Complete with 5.5 mM glucose 6.0 mM alanine 4.0 mM lactate 1.0 mM citrate	1.10
Without glucose	0.98
Without alanine	0.88
Without any organic solutes	0.56

In all cases the bathing solution was an artificial solution resembling serum and contained all of the organic solutes plus 6 g/dl bovine serum albumin. Data are from Burg et al. (7).

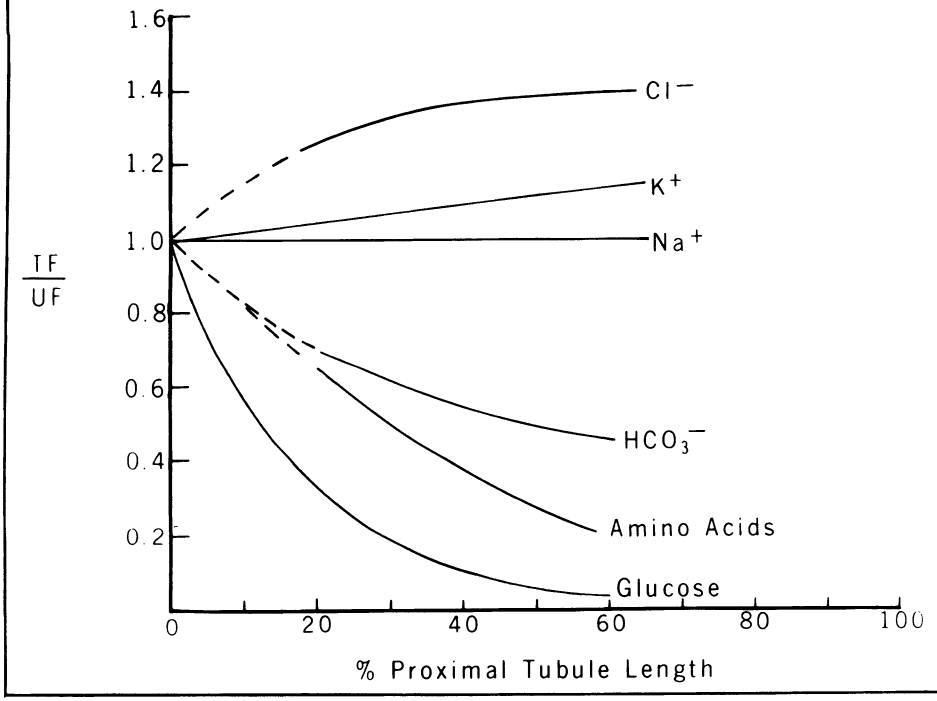

Figure 3.
Change in tubular fluid solute concentrations along proximal tubule. Ratio of solute concentration in tubular fluid to that in an ultrafiltrate of plasma (FT/UF) is plotted as a function of distance, which is expressed as a percentage of total proximal tubule length. Data are from experiments involving micropuncture collections from accessible regions of rat proximal convoluted tubule: Cl^- (14); Na^+ (11, 13); K^+ (7); HCO_3^- (14, 22); amino acids (9); and glucose (25). Since these data have been collected from different laboratories and in some cases involve different experimental protocols, plots should not be taken to provide an accurate mapping of solute absorption. Rather they are intended to indicate relative rates of absorption for various solutes and resulting change in tubular fluid composition.

tubule from the glomerulus to the late portion of the proximal convoluted tubule. These data from the rat show that although the concentration of sodium remains relatively constant, the concentrations of the preferentially absorbed solutes (i.e., bicarbonate, amino acids, glucose, and organic acids) decrease along the proximal convoluted tubule, while the concentrations of chloride and even potassium rise. I have included these data not only to demonstrate the rapid active absorption of certain solutes in the proximal tubule but, more importantly, to indicate that very early in the proximal convoluted tubule the composition of the tubular fluid becomes significantly different from that of an ultrafiltrate of plasma. When this tubular fluid is sampled and analyzed, its osmolality is determined by its freezing-point depression, and the result one obtains may be called an *absolute* osmolality. However, especially in a leaky epithelium such as the proximal tubule, solutes may have differing reflection coefficients, so that the absolute osmolality of a solution may not be indicative of its osmotic effectiveness. For this reason, I will use a modified term, the *effective* osmolality difference. Simply defined, this term is meant to indicate that osmolality difference which can produce an osmotic volume flow. For each individual solute the effective osmolality difference is given by the reflection coefficient for the solute times the difference in concentration, $\sigma\Delta C$. When one considers the difference in osmolality between two complex solutions such as tubular fluid and interstitial fluid. then the total effective osmolality difference is given by the sum of the products of the reflection coefficient and concentration difference for each of the individual solutes

$$\text{effective osmolality difference} = \Sigma\sigma_i\Delta C_i$$

The important point here is that although the tubular fluid may have a cryoscopic or *absolute* osmolality identical or even higher than that of the plasma, it may have an effective osmolality lower than that of plasma if the tubular fluid contains predominantly solutes with lower reflection coefficients.

I would now like to turn to some experiments designed to demonstrate the existence of such *effective* osmotic driving forces. In these experiments, we used segments of rabbit proximal tubules, primarily proximal straight tubules, which were perfused in vitro with solutions of differing composition. The primary parameter that we measured was the rate of volume absorption. In the first experiment we wanted to demonstrate the existence of an effective osmotic driving force when there were gradients of bicarbonate and chloride across the epithelium as are known to exist in the late proximal convoluted tubule and in the proximal straight tubule (see Fig. 3). We perfused the tubules with a solution containing a high concentration of sodium chloride but a low concentration of sodium bicarbonate. The bathing solution resembled serum with a higher sodium bicarbonate concentration, but it should be noted that both solutions had the same measured *absolute* osmolality of 290 mosmol/l. We perfused these tubules at rates of 4–40 nl/min, and ouabain, in some cases, was added to eliminate active solute absorption.

The results of these experiments are shown in Fig. 4. The volume absorption rate is plotted as a function of the perfusion rate when the tubules were perfused with the high chloride solution, so that there was a gradient chloride concentration from the lumen to the bathing solution and an opposing bicarbonate gradient (28, 32). In control tubules, we observed that there was a direct relationship between the rate of volume absorption and the perfusion rate. Furthermore, when we added ouabain to remove active solute absorption, the volume absorption was diminished but not to zero, and the remaining volume absorption was dependent on the perfusion rate. Similar experiments have also been conducted in the rat proximal convoluted tubule perfused in vivo with comparable results (27). We would interpret the continuation of volume absorption in the presence of ouabain to indicate that the water flow under these circumstances is being driven by an effective osmolality gradient which is produced as a consequence of the fact that bicarbonate has a higher reflection coefficient than

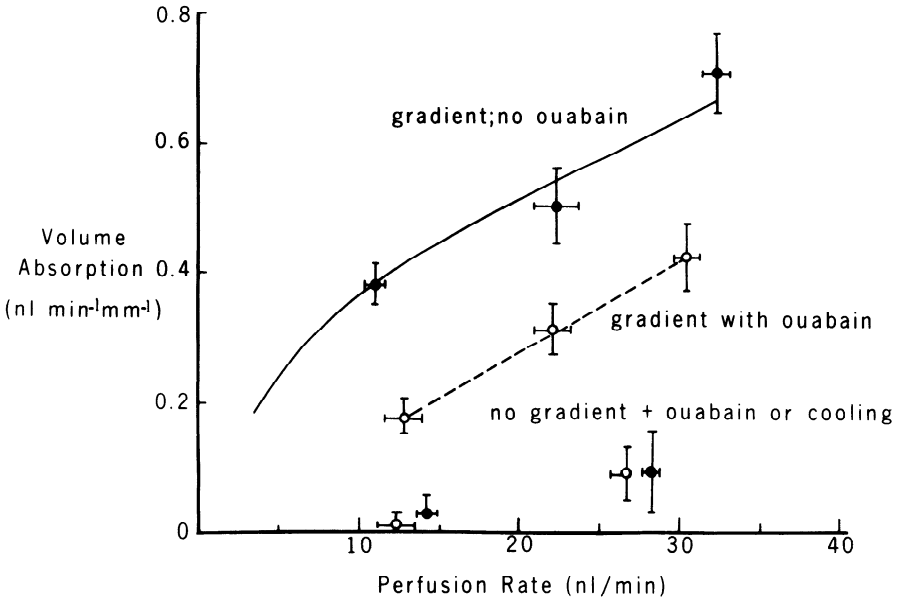

Figure 4.
Volume absorption in proximal straight tubule in presence and absence of transepithelial anion concentration gradients. *Upper two curves* show dependence of volume absorption on perfusion rate for isolated proximal straight tubules perfused with a solution containing Cl^- as primary anion and no HCO_3^-. Since bathing solution contained normal plasmalike concentrations of Cl^- (110 mM) and HCO_3^- (25 mM), there were transepithelial anion concentration gradients in upper two curves as indicated by gradient. In *lower curve* (*dashed line, open dots*), 0.1 mM ouabain was added to bathing solution to inhibit active solute absorption. Tubules were also perfused at 10–15 or 25–30 nl/min under conditions when no transepithelial Cl^- and HCO_3^- concentration gradients were present (*lower four points*) and active transport was inhibited by ouabain or cooling to 21–23 °C. Data from Schafer et al. (32). See also Refs. 10 and 27.

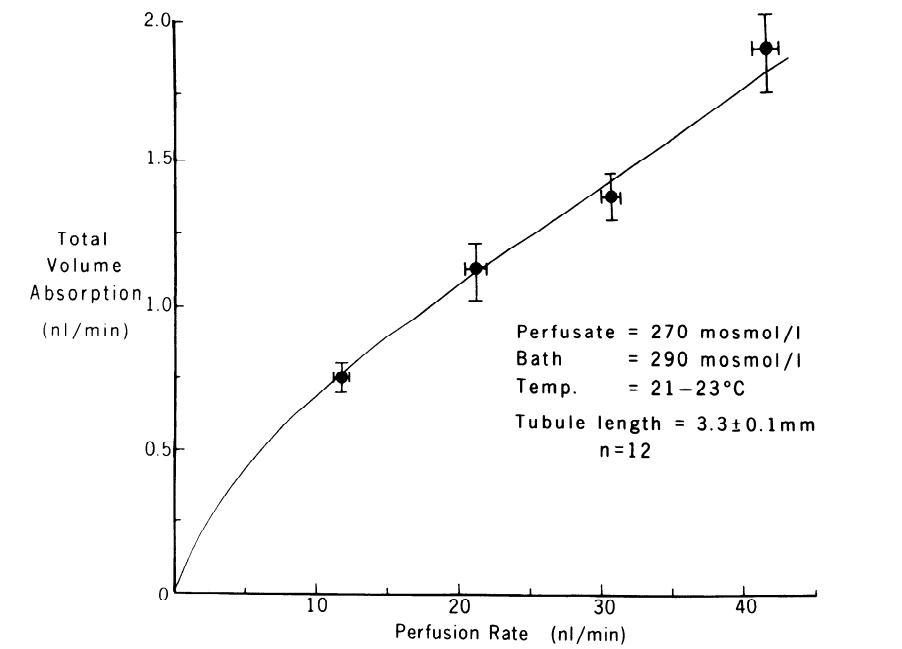

Figure 5.
Dependence of volume absorption on perfusion rate in isolated proximal straight tubules. Tubule segments were perfused at varying rates with a hypoosmotic solution while being bathed by an isosmotic solution. Temperature was kept at 21–23 °C to prevent active solute absorption. Data of Schafer et al. (30).

chloride and thus the perfusate is effectively hyposmotic to the bathing solution. This conclusion is supported by the fact that if the anion gradients are removed either by adding chloride in place of bicarbonate in the bathing solution or by adding bicarbonate to the perfusate in place of chloride, then there is no net volume absorption in the presence of ouabain at any perfusion rate (28, 32).

It is somewhat more difficult to explain the dependence of volume absorption on the perfusion rate as we observe in the presence of the anion gradients. Our interpretation of this phenomenon is that osmotic equilibration occurs rapidly in the proximal tubule due to its high hydraulic conductivity. At more rapid perfusion rates, osmotic equilibration would be delayed and the total volume absorption would be greater. This concept is elusive at first and I would like to illustrate it by means of a simpler experiment.

In this experiment we perfused proximal straight tubules with a simplified sodium chloride solution that was hypoosmotic, having a measured osmolality of only 270 mosmol/l. The bathing solution, however, had an osmolality of 290; and therefore there was an *absolute* osmolality difference between the tubular fluid and the bathing solution. We then measured volume absorption under conditions where we varied the perfusion rate at room temperature. The results of these experiments are shown in Fig. 5. The volume absorption is plotted as a function of the perfusion rate. The tubules we perfused all had a length of about 3.3 mm. Remember that the perfusate is 270 mosmol/l and the bathing solution 290 mosmol/l, and that there is no active volume absorption because the temperature is 21–23° C. It can be seen that there was an increase in volume absorption as the perfusion rate increased.

The explanation for the observations in Fig. 5 is as follows. When the hypoosmotic perfusate moves along the tubular lumen, osmotic equilibration occurs as water moves out and, to a lesser extent, solute moves into the lumen. At a slow perfusion rate, osmotic equilibration occurs early along the tubule length, but at

a more rapid perfusion rate the osmotic equilibration rate is delayed. Consequently, the total volume absorption along the same perfused segment will be greater at a more rapid perfusion rate. To make the concept clearer, we developed a mathematical model to predict the changes in tubular fluid osmolality and volume absorption along the perfused tubule in an experiment like that shown in Fig. 5 (for details, see Refs. 30, 32).

In Fig. 6 the luminal osmolality and the volume absorption rate are plotted as a function of distance along the perfused tubule. The results of the model were calculated for an osmotic water permeability of 3,000 μm/s at perfusion rates of 10 or 40 nl/min. As in the experiments above, the luminal perfusate was initially hypotonic at 270 mosmol/l, but the model predicts that it would become rapidly isosmotic due to volume flow out. As a consequence of this, the volume absorption rate would fall to zero in less than 1 mm of the perfused length at the slower perfusion rate. However, with an increased perfusion rate, the osmotic equilibration is delayed along the tubular length and volume absorption continues at a higher rate along a greater length of the perfused segment (30).

A similar mathematical model can also be applied to the situation where the perfusate and bathing solution have the same absolute osmolalities, but when the perfusate has an elevated chloride and a lower bicarbonate concentration, i.e., the experiment shown in Fig. 4 above. In Fig. 7 the luminal osmolality is depicted as a function of the tubule length. The absolute osmolality of the bathing solution is 290 mosmol/l as is the *initial* perfusate. In this situation there are gradients of bicarbonate and chloride across the tubule epithelium. As a consequence of the higher luminal chloride and lower bicarbonate concentrations, the luminal perfusate is *effectively* hypoosmotic. Due to the resulting water flow outward, the luminal osmolality rises rapidly and volume flow stops when the effective osmolality of the tubular fluid is equal to that of the bathing solution. However, this occurs only when the absolute osmolality of the luminal fluid is greater than that of the bathing solution. If the perfusion rate were increased, the osmotic equilibration would be delayed along the tubular length, and a greater total volume absorption would result. In the presence of ouabain, when there is no active solute transport, the volume absorption would be predicted to *stop* when the absolute luminal osmolality had risen by about 6 mM. However, in the presence of active solute absorption, the perfusate could be maintained *effectively* hypoosmotic by about 1–2 mosmol/l. The same analysis can be applied to the results of in vivo perfusion experiments in the rat proximal convoluted tubule for which Giebisch et al. (10) also observe flow-dependent volume absorption in the absence of active transport but with transepithelial Cl^- and HCO_3^- concentration gradients present.

The absorption of volume in the presence of anion concentration gradients but in the absence of solute transport has often been referred to as "passive" volume absorption. However, the results in Fig. 7 show that passive volume absorption would be limited to only a short segment of the proximal tubule before osmotic equilibration had occurred and volume absorption would stop. Therefore, continued volume absorption is dependent on the presence of active solute absorption.

In the late proximal nephron, after the luminal concentration of bicarbonate and organic solutes have been reduced to minimal levels, we feel that the remaining active solute absorption is due to simple, rheogenic sodium absorption. To demonstrate the existence of a simple rheogenic sodium absorption mechanism, we performed the following experiments. Segments of isolated proximal straight tubules were perfused and bathed with a simple sodium chloride solution that contained no organic solutes or bicarbonate. Both perfusate and bathing solution were gassed with pure oxygen. In this situation, continued volume absorption must depend on the development of *absolute* luminal hypoosmolality not the development of solute asymmetry

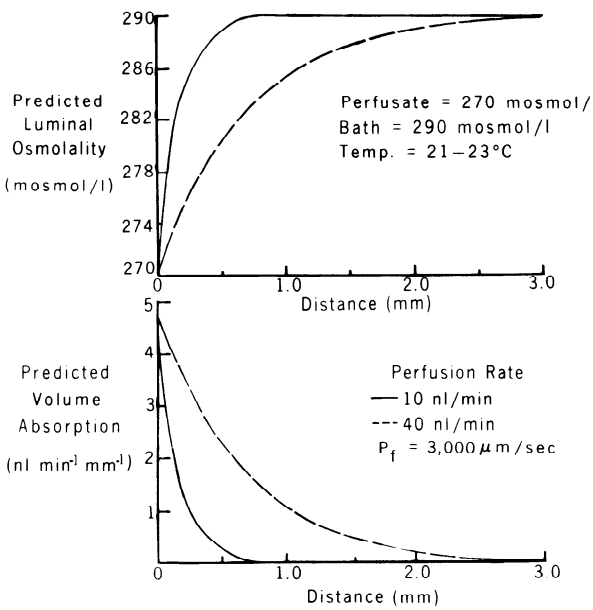

Figure 6.
Luminal osmolality and volume absorption along the length of a tubule segment as predicted from a mathematical model of osmotic equilibration. The mathematical model was applied to the analysis of the experiment described in the legend to Fig. 5 assuming an osmotic water permeability of 3,000 μm/s. From Schafer et al. (30).

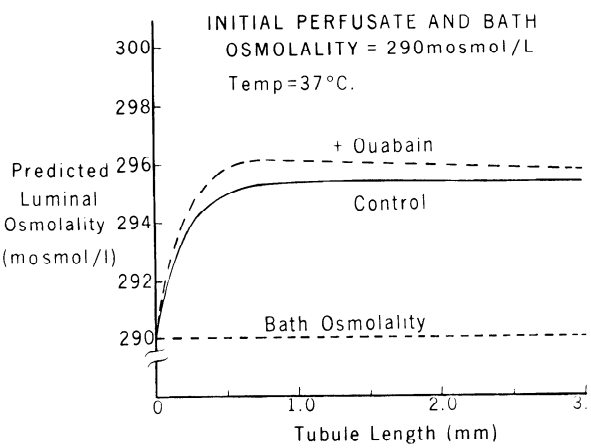

Figure 7.
Luminal osmolality along length of a tubule segment as predicted by a mathematical model. Model was applied to experimental situation described in legend to Fig. 4 in presence and absence of 0.1 mM ouabain in bathing solution. See Schafer et al. (32) for details.

between the perfusate and bath. Table 4 presents the measured volume absorption and the transepithelial voltage in mV from these experiments. In spite of the absence of bicarbonate or organic solutes in the aqueous solutions, there was significant volume absorption which was inhibited completely by ouabain but not by the carbonic anhydrase inhibitor ethoxzolamide.

From the experiments discussed above we have drawn the following conclusions regarding the mechanism of volume absorption in the proximal nephron. First, along the entire length of the proximal nephron, volume absorption depends on the development of effective hypoosmolality of the tubular fluid. In the early proximal tubule, the rapid absorption of sodium bicarbonate and organic solutes can produce *absolute* hypoosmolality of the tubular fluid. In the late proximal tubule, gradients have developed for bicarbonate and the organic solutes which can lead to the development of absolute luminal *hyper*-osmolality but *effective hypo*-osmolality due to the higher reflection coefficients for bicarbonate and organic solutes. Finally, the maintenance of the effective luminal hypoosmolality along the entire proximal tubule depends upon continued active solute absorption.

Return of Absorbed Water and Solutes to Peritubular Capillaries

The final and necessary step in the absorption of salt and water in the proximal nephron is the return of the absorbed substances to the circulation via the peritubular capillaries. In the context of this brief review, it is impossible to discuss this aspect of salt and water absorption to the extent that is actually warranted. Therefore, this section is intended merely to point out the important parameters that determine the peritubular capillary uptake of solute and water. The article concludes with a brief mention of factors that may be involved in the regulation of solute and water absorption in the proximal nephron.

Fluid uptake into peritubular capillaries is determined by the same Starling forces that determine fluid transfer across all capillaries and are summarized by the equation

$$\text{fluid uptake into capillaries} = K_F[P_C - P_I - (\Pi_C - \Pi_I)]$$

The uptake is dependent on the term K_F, the capillary filtration coefficent, which is a combination of the hydraulic conductivity of the capillary endothelium as well as its total surface area. Present measurements indicate that this parameter is actually larger for peritubular capillaries than for glomerular capillaries (21, 39). The capillary uptake is also directly dependent on the difference between the interstitial (P_I) and capillary (P_C) hydrostatic pressures and the difference between the interstitial (Π_I) and capillary (Π_C) colloid osmotic pressures. Unfortunately, there are considerable methodological difficulties in obtaining reliable estimates of these parameters. The best available evidence has been summarized recently by Navar et al. (21) and Wolgast et al. (39) as shown in Table 5. The estimates indicate that under control conditions the total pressure tending to drive uptake into the capillaries far exceeds that opposing the uptake. However, the balance of these forces may be an important determinant of the rate of volume absorption by the proximal tubule. For example, it might be expected if the capillary colloid osmotic pressure were diminished by dilution during isotonic volume expansion that capillary uptake should also be diminished with a resulting increase in interstitial pressure. An increase in interstitial fluid pressure or a decrease in interstitial colloid osmotic pressure might in turn decrease volume absorption across the proximal tubule epithelium. The effects of changes in these parameters have been referred to as peritubular factors. However, the mechanism and the importance of these effects in proximal tubular volume absorption is presently uncertain.

Table 4

Volume Absorption in Absence of Preferentially Absorbed Solutes in Perfusate

Inhibitor	Volume Absorption $nl \cdot min^{-1} \cdot mm^{-1}$	Transepithelial Voltage, mV
None	0.20 ± 0.02	−0.9 ± 0.2
10^{-4} M ouabain	−0.02 ± 0.01	+0.02 ± 0.2
0.16 mM ethoxzolamide	0.22 ± 0.03	−0.7 ± 0.2

Tubules were perfused and bathed with simple phosphate-buffered NaCl solutions. Perfusate contained no glucose, amino acids, organic acids, or bicarbonate. Bathing solution was bubbled with pure O_2. Transepithelial voltage reported here is the displacement from the calculated Donnan voltage of +2.36 mV. From Schafer et al. (31).

Table 5

Forces Governing Fluid Uptake by Peritubular Capillaries

Factors Favoring Uptake	mmHg	Factors Opposing Uptake	mmHg
Π_C	20–32	Π_I	2–10
P_I	2–4	P_C	12–17
Total	22–36	Total	14–22

Π, colloid osmotic pressure; P, hydrostatic pressure; C, capillary; I, interstitial. From Navar et al. (21); Wolgast et al. (39).

Wolgast et al. (39) have recently assembled data from the literature in which interstitial osmotic and hydrostatic pressures have been measured under conditions of antidiuresis, saline expansion, or plasma expansion. Although the difference between the interstitial osmotic and hydrostatic pressures varied widely, there was little change in the rate of proximal tubular fluid absorption. Thus although these peritubular factors should be very important determinants of proximal tubule volume absorption, it would appear that the appropriate means of studying changes in these factors associated with physiological control of volume absorption have not as yet been developed.

Finally, we also need more information about the mechanisms by which salt and water absorption may be regulated by humoral and neural factors and the mechanism by which proximal volume absorption is adjusted during variations in the rate of filtration. It is known that sympathetic nerve fibers have endings associated with the basement membranes of proximal and distal tubules, and synapses with tubular cells have

been described (4). There is presently a considerable amount of information that α-adrenergic input has an antinatriuretic effect and β-adrenergic input has a diuretic effect (16). However, it has also been shown that in isolated perfused proximal convoluted tubules the application of norepinepherine in the bathing solution results in enhanced volume absorption which can be blocked by propranalol (6). The role of these humoral agents and sympathetic input in the physiological control of proximal salt and water absorption remains unknown.

A final issue, which is beyond the scope of this tutorial lecture, is the process of glomerulotubular balance, i.e., the normal adjustment of proximal tubule volume absorption to a constant fraction of the glomerular filtration rate. The normal mechanisms by which these adjustments in proximal tubule volume absorption may be made, and which may be altered under conditions where the fractional volume absorption of the proximal tubule changes, are certainly important considerations in the regulation of fluid balance by the proximal tubule and the kidney as a whole.

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References

1. Altman, P.L., and D.S. Dittmer (Editors). *Biology Data Book* (2nd ed.). Bethesda, MD: FASEB, 1974, vol. III, p. 1786.

2. Andreoli, T.E., J.A. Schafer, and S.L. Troutman. Perfusion rate-dependence of transepithelial osmosis in isolated proximal convoluted tubules: estimation of the hydraulic conductance. *Kidney Int.* 14: 263-269, 1978.

3. Andreoli, T.E., J.A. Schafer, S.L. Troutman, and M.L. Watkins. Solvent drag component of Cl^- flux in superficial proximal straight tubules: evidence for a paracellular component of isotonic fluid absorption. *Am. J. Physiol.* 237 (*Renal Fluid Electrolyte Physiol.* 6): F455-F462, 1979.

4. Barajas, L., and J. Muller. The innervation of the juxtaglomerular apparatus and surrounding tubules: a quantitative analysis by serial section electron microscopy. *J. Ultrastruct. Res.* 43: 107-132, 1973.

5. Barratt, L.J., J.D. Wallin, F.C. Rector, Jr., and D.W. Seldin. Influence of volume expansion on single-nephron filtration rate and plasma flow rate in the rat. *Am. J. Physiol.* 224: 643-650, 1973.

6. Bello-Reuss, E. Effect of catecholamines on fluid reabsorption by the isolated proximal convoluted tubule. *Am. J. Physiol.* 238 (*Renal Fluid Electrolyte Physiol.* 7): F347-F352, 1980.

7. Burg, M.B., C.S. Patlak, N. Green, and D. Villey. Organic solutes in fluid absorption by renal proximal convoluted tubules. *Am. J. Physiol.* 231: 627-637, 1976.

8. Diamond, J.M., and W.H. Bossert. Standing-gradient osmotic flow. A mechanism for coupling of water and solute transport in epithelia. *J. Gen. Physiol.* 50: 2061-2083, 1967.

9. Eisenbach, G.M., M. Weise, and H. Stolte. Amino acid reabsorption in the rat nephron. Free flow microuncture study. *Pfluegers Arch.* 357: 63-76, 1975.

10. Giebisch, G., R.J. Moriarty, and R. Green. Active and passive components of flow-dependent fluid transport across proximal convoluted rat tubule (Abstract). *Clin. Res.* 26: 497A, 1979.

11. Giebisch, G., and E.E. Windhager. Electrolyte transport across renal tubular membranes. In: *Handbook of Physiology. Renal Physiology.* Washington, DC: Am. Physiol. Soc., 1973, sect. 8, chapt. 11, p. 315-376.

12. Giebisch, G., and E.E. Windhager. Renal tubular transfer of sodium, chloride and potassium. *Am. J. Med.* 36: 643-669, 1964.

13. Gottschalk, C.W. Renal tubular function: lessons from micropuncture. *Harvey Lect. Ser. B* 58: 99-124, 1962-63.

14. Gottschalk, C.W., W. Lassiter, and M. Mylle. Localization of urine acidification in the mammalian kidney. *Am. J. Physiol.* 198: 581-585, 1960.

15. Gottschalk, C.W., and M. Mylle. Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the countercurrent hypothesis. *Am J. Physiol.* 196: 927-936, 1959.

16. Kim, J.K., S.L. Linas, and R.W. Schrier. Catecholamines and sodium transport in the kidney. *Pharmacol. Rev.* 31: 169-178, 1980.

17. Kyte, J. Immunoferritin determination of the distribution of (Na^+ and K^+) ATPase over the plasma membranes of renal convoluted tubules. II. Proximal segment. *J. Cell Biol.* 68: 304-318, 1976.

18. LeGrimellec, C. Micropuncture study along the proximal convoluted tubule. Electrolyte reabsorption in first convolutions. *Pfluegers Arch.* 354: 133-150, 1975.

19. Murer, H., H. Hopfer, and R. Kinne. Sodium/proton antiport in brush-border membrane vesicles isolated from rat small intestine and kidney. *Biochem. J.* 154: 597-604, 1976.

20. Murer, H., and R. Kinne. The use of isolated membrane vesicles to study epithelial transport processes. *J. Membr. Biol.* 55: 81-95. 1980.

21. Navar, L.G., A.P. Evan, and L. Rosivall. Microcirculatory dynamics in the kidney. In: *The Physiology and Pharmacology of the Microcirculation,* edited by N. Mortillaro. New York: Academic. In press.

22. Rector, F.C., Jr., N.W. Carter, and D.W. Seldin. The mechanism of bicarbonate reabsorption in the proximal and distal tubules of the kidney. *J. Clin. Invest.* 44: 278-290, 1965.

23. Renkin, E.M., and J.P. Gilmore. Glomerular filtration. In: *Handbook of Physiology. Renal Physiology.* Washington, DC: Am. Physiol. Soc., 1973, sect. 8, chapt. 9, p. 185-248.

24. Ringler, D.H., and L. Dabick. Hematology and clinical biochemistry. In: *The Laboratory Rat,* edited by H.J. Baker, J.R. Lindsey, and S.H. Weisborth. New York: Academic, 1979, vol. I, p. 105-121.

25. Rohde, R., and P. Deetjen. Glucose reabsorption in the rat kidney. Micropuncture analysis of tubular glucose concentration during free flow. *Pfluegers Arch.* 302: 219-232, 1968.

26. Sacktor, B. Mechanisms and specificities of amino acid transport in proximal tubule luminal membrane vesicles. In: *Renal Function,* edited by G.H. Giebisch and E.F. Purcell. New York: Josiah Macy Jr. Found., 1978. p. 221-229.

27. Schafer, J.A., and T.E. Andreoli. Driving forces for volume absorption along the proximal nephron. *Jpn. J. Nephrol.* 23: 965-972, 1981.

28. Schafer, J.A., C.S. Patlak, and T.E. Andreoli. A component of fluid absorption linked to passive ion flows in the superficial pars recta. *J. Gen. Physiol.* 66: 445-471, 1975.

29. Schafer, J.A., C.S. Patlak, and T.E. Andreoli. Fluid absorption and active and passive ion flows in the rabbit superficial pars recta. *Am. J. Physiol.* 223 (*Renal Fluid Electrolyte Physiol.* 2): F154-F167, 1977.

30. Schafer, J.A., C.S. Patlak, S.L. Troutman, and T.E. Andreoli. Volume absorption in the pars recta. II. Hydraulic conductivity coefficient. *Am. J. Physiol.* 234: (*Renal Fluid Electrolyte Physiol.* 3): F340-F348, 1978.

31. Schafer, J.A., S.L. Troutman, M.L. Watkins, and T.E. Andreoli. Volume absorption in the pars recta. I. "Simple" active Na^+ transport. *Am. J. Physiol.* 234: (*Renal Fluid Electrolyte Physiol.* 3): F332-F339, 1978.

32. Schafer, J.A., S.L. Troutman, M.L. Watkins, and T.E. Andreoli. Flow dependence of fluid transport in the isolated pars recta. *Kidney Int.* In press.

33. Shindo, T., and K.R. Spring. Chloride movement across the basolateral membrane of proximal tubule cells. *J. Membr. Biol.* 58: 35-42, 1981.

34. Smith, H.W. The excretion of water. *Bull. NY Acad. Med.* 23: 177, 1947.

35. Smith, H.W. *The Kidney. Structure and Function in Health and Disease.* New York: Oxford Univ. Press, 1951. p. 309-327.

36. Ullrich, K.J. Sugar, amino acid, and Na^+ cotransport in the proximal tubule. *Annu. Rev. Physiol.* 41:181-195, 1979.

37. Warnock, D.G., and V.J. Yee. Chloride uptake by brush border mmmbrane vesicles isolated from rabbit renal cortex. *J. Clin. Invest.* 67: 103-115, 1981.

38. Welling, L.W., and D.J. Welling. Shape of epithelial cells and intercellular channels in the rabbit proximal nephron. *Kidney Int.* 9: 385-394, 1976.

39. Wolgast, M., M. Larson, and K. Nygren. Functional characteristics of the renal interstitium. *Am. J. Physiol.* 241 (*Renal Fluid Electrolyte Physiol.* 10): F105-F111, 1981.

Developmental Renal Physiology

LEONARD I. KLEINMAN
Department of Pediatrics and Physiology
University of Cincinnati
College of Medicine
Cincinnati, Ohio 45267

The mammalian kidney develops through three successive but overlapping stages: the pronephros, the mesonephros, and the metanephros. The definitive mammalian kidney, the metanephros, develops from the union of the cranial part of the ureteral bud with the metanephric blastema. The ureteral bud arises from an offshoot of the mesonephric duct and ultimately forms the ureters, renal pelvis, major and minor calyces, and collecting ducts. The nephroblastic cells of the metanephric blastema, on contact with the ureteral bud, eventually develop into the glomerulus, proximal convoluted tubule, loop of Henle, and distal convoluted tubule.

The first nephrons to develop are those the glomeruli of which will be found in the juxtamedullary region of the mature kidney. At 22 wk gestation (term is 40 wk), all the glomeruli in the human fetus are juxtamedullary glomeruli. Since nephron development starts in the juxtamedullary region and progresses centrifugally toward the capsule, at anytime during development there is a greater percentage of mature nephrons in the juxtamedullary region than in the outer cortex.

The metanephric kidney undergoes three basic phases of growth, with a good deal of overlap among these phases. The first phase is that of nephrogenesis (the development of new nephrons), which ceases at various stages of development in different species. In the human, nephrogenesis is complete at 36 wk fetal gestation (24), so that a full-term newborn infant has as many nephrons as he will have for the rest of his life, but a prematurely born infant will continue to produce new nephrons for sometime after birth. Similarly, nephrogenesis is complete before birth in the fetal sheep (29) and guinea pig (33). On the other hand, nephrogenesis continues after birth for about 2 wk in the dog (19), 3 wk in the pig (8), and 4–6 wk in the rat (32).

The second phase of growth is the anatomical maturation of the nephrons already present. Thus there are changes in glomerular and tubular histology that could theoretically affect renal function. Included in this phase of renal growth are biochemical and enzymatic changes in the renal cells. The final phase of renal development is that of growth of the nephron with no apparent histological or biochemical maturation. However, in this phase of growth, glomeruli and tubules, proximal and distal tubules, superficial and juxtamedullary nephrons do not necessarily develop at the same rate, creating changing balance in function of these portions of the kidney.

Although the basic techniques used in studying renal function ought to be the same for the developing animal as they are for the adult, the very nature of the developing perinatal animal introduces problems that are not encountered in the adult. For example, the fetus is not readily accessible. Early studies on fetal kidneys utilized exteriorized fetal preparations that were highly unphysiological. More recently, chronically catheterized in situ fetal preparations have been utilized, particularly the fetal lamb (27, 28). Another problem in studying renal function in developing animals is that one of the most useful techniques in renal physiology, micropuncture, cannot be used during certain parts of development. As mentioned earlier the most superficial nephrons are the least mature; indeed in certain species, the dog and rat for example, at certain times of development the superficial nephrons are nonfunctioning and micropuncture cannot be utilized at all. Even during those periods when the superficial nephrons are functioning, their function and rate of development do not necessarily reflect that of the rest of the kidney. Therefore alternative techniques must be used utilized to study the segmental localization of renal functional development. Finally, because the kidney of the developing animal is growing, it is important to relate any change in function to the change in growth. Unfortunately, not all investigators have normalized developmental renal functions to the same growth parameter, making it difficult for a reviewer to compare results obtained in different laboratories. For the purpose of the present discussion, kidney weight is used as the primary growth parameter. Moreover, when developmental patterns are compared from one species to another, it is important for a reviewer to be cognizant of the different phases of renal growth for the various species mentioned previously.

It is not possible in this limited space to discuss all aspects of renal developmental physiology; so the discussion will be limited to two topics: *1*) the development of renal blood flow and glomerular filtration rate and *2*) the development of sodium excretion.

Development of Renal Blood Flow and Glomerular Filtration Rate

Blood flow to the kidney does not develop in a homogeneous pattern. Figure 1 reveals the maturational characteristics of blood flow to the inner and outer cortex of the newborn dog (19). Blood flow to the outer cortical region increases continuously with age (corrected for renal mass in this region), whereas inner cortical flow changes little at first (again corrected for regional renal mass) and then increases with age. Another way to evaluate the maturational pattern of intrarenal blood flow is to look at the relative flows to the two different regions, i.e., the developmental characteristics of the ratio of blood flow to the inner and outer cortex (Fig. 2). Early in life the ratio of inner to

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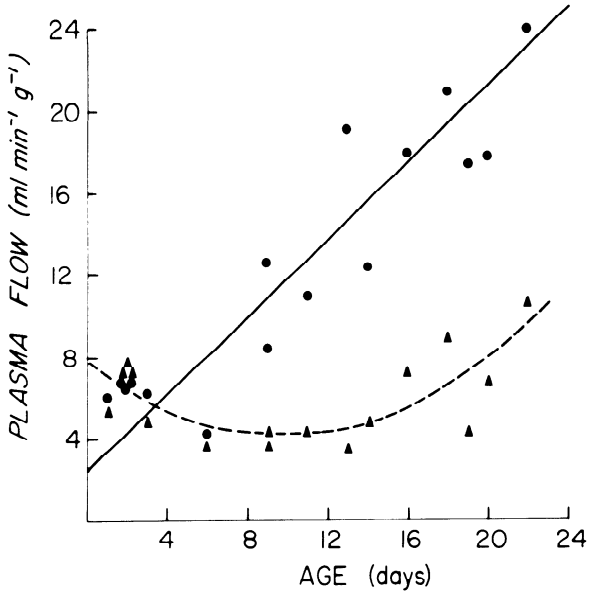


Figure 1
Maturation of plasma flow to outer cortex (•———•) and inner cortex (▲- - -▲) of kidney of newborn dogs. Flow to each region of the kidney is factored by dry mass of the region. [From Ref. 19]

outer cortical blood flow is approximately one, and during the first 2 wk the ratio declines (due primarily to the increase in outer cortical flow, Fig. 1) and then remains constant thereafter. Note that in the case of the neonatal dog the developmental change in relative intrarenal blood flow distribution occurs during the period of nephrogenesis and ceases at 2 wk after birth when nephrogenesis is complete. This correlation of intrarenal blood flow distribution maturation to anatomical maturation does not hold for all animals studied, however (29).

With regard to the whole kidney, renal blood flow (RBF) is continuously increasing, but so is renal mass. In the fetal lamb, the increase in renal growth and renal blood flow occur at approximately the same rate, so that renal blood flow per unit kidney mass does not change (28). However, after birth renal blood flow increases at a greater rate than kidney mass.

Changes in glomerular filtration rate (GFR) parallel those for renal blood flow both in terms of intrarenal distribution and whole-kidney development. Thus glomerular filtration at a certain stage of development is lower in the outer than inner cortex but then increases at a greater rate in the outer than in the inner cortex (33). With regard to the whole kidney, GFR increases as the animal matures, but as in the case of renal blood flow, the relative rates of increase for GFR and kidney mass depend on the stage of development.

Based on studies of different species it is possible to define three stages of GFR development. These functional stages, however, do not necessarily correlate with the anatomical phases mentioned previously. It is important, nevertheless, to be aware of these different functional stages when comparing results from one species to another. The first stage, exemplified by the fetal lamb, is characterized by equivalent rates of increases of GFR and kidney mass, so that there is no change with age in GFR per gram kidney (Fig. 3). The second stage, exemplified by the newborn dog (Fig. 4) [but also by the human infant during the first 4 mo of life (30), the neonatal lamb during the first 2 mo of life (2), the neonatal piglet during the first 2 mo (7), and the rat for the first 40–50 days of life (12)], is characterized by a greater rate of increase in GFR than in kidney growth. Thus, GFR per gram kidney weight is increasing during this period. In the final phase of development glomerular filtration increases at the same rate as that of kidney mass.

Analysis of mechanisms of RBF and GFR development are made difficult by these three different stages of development which, as mentioned above, do not necessarily correlate with the three different phases of anatomical growth. Nevertheless, it may be possible to clarify some of these mechanisms based on a multitude of studies from various species at different stages of development. Summarized in Table 1 are the patterns of development of renal growth, RBF, GFR, and factors that might affect RBF, GFR, such as arterial blood pressure, renal vascular resistance, glomerular capsular

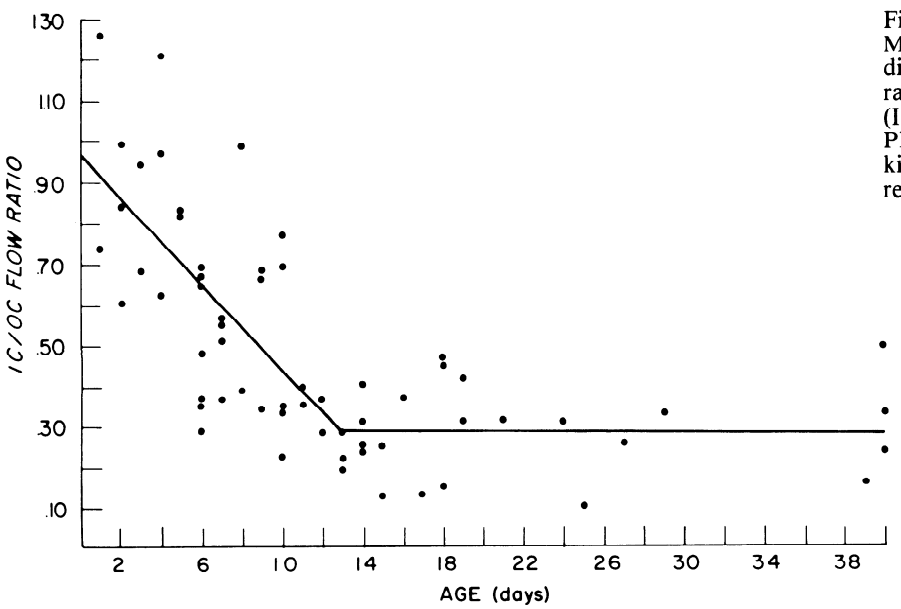


Figure 2
Maturation of intrarenal blood flow distribution in newborn dog. IC/OC, ratio of plasma flow of inner cortex (IC) to that of outer cortex (OC). Plasma flow to each region of the kidney is factored by dry mass of the region. [From Ref. 19]

Figure 3
Maturation of glomerular filtration rate (GFR) in fetal lamb. GFR is expressed in units of ml/min (————) and units of ml•min^{-1}•g kidney wt^{-1} (- - -). Rate of kidney growth is also known (— —). [From data of Robillard et al. (28)]

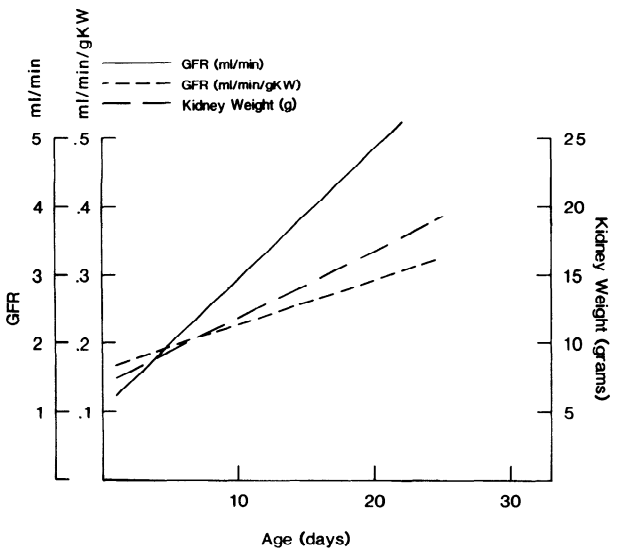
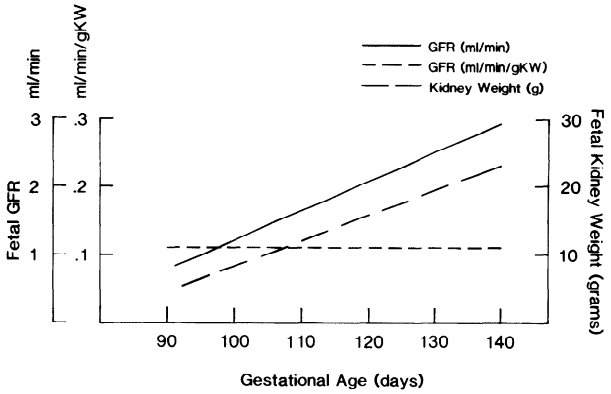


Figure 4
Maturation of glomerular filtration rate (GFR) in neonate dog. GFR is expressed in units of ml/min (————) and units of ml•min^{-1}•g kidney wt^{-1} (- - -). Rate of growth is also shown (— —). [From data of Kleinman and Lubbe (18)]



hydrostatic pressure (P_{GC}), individual glomerular plasma flow (GPF), and filtration coefficient (K_F).

The two primary factors that affect renal blood flow are blood pressure and renal vascular resistance. In the early period in the fetal lamb there is only a slight increase in blood pressure and a marked decrease in renal vascular resistance with maturation (29), so that the rise in total renal blood flow during this period is clearly due to the change in renal vascular resistance. However, the change in vascular resistance is parallel to the change in renal growth; so there is little or no change in renal vascular resistance per unit renal mass and little or no change in renal blood flow per gram kidney.

Blood pressure rises during the second developmental period (18). Although renal vascular resistance falls during this period in all species studied, there is controversy about the change in vascular resistance per unit renal mass. In the pig (9), guinea pig (33), and some studies in dogs (14) vascular resistance per gram kidney has been shown to fall with maturation; in other studies in dogs there is no change (18), and in the rhesus monkey it actually rises slightly (6). Thus the increase in renal blood flow per kidney mass during this period is probably related to the increase in blood pressure and perhaps (in certain species at least) to the fall in renal vascular resistance.

Factors determining the rate of glomerular filtration include glomerular plasma flow, plasma oncotic pressure, glomerular capillary hydrostatic pressure, capsular hydrostatic pressure, and the glomerular filtration coefficient. The relative contribution of each of these factors is dependent on whether there is filtration equilibrium. Filtration equilibrium will exist if there is no net force for filtration at the end of the glomerular capillary. Filtration equilibrium occurs in certain strains of rats but does not occur in other rat strains or in dogs. However, filtration equilibrium is more likely to occur in any species at relatively lower glomerular capillary hydrostatic pressures and higher filtration coefficients. In the presence of filtration equilibrium, changes in K_F have little effect, and is a very important determinant of GFR. In the absence of filtration equilibrium K_F plays a more important and GPF a less important role in determining GFR. P_{GC} affects GFR whether or not there is filtration equilibrium.

It is not known whether filtration equilibrium exists in the developing kidney. On the one hand the lower blood pressure and/or higher renal vascular resistance [and consequently lower glomerular hydrostatic pressure (1)], favor its existence; on the other hand the smaller size and lower surface area [and therefore lower K_F] might tend to interfere with filtration equilibrium. In the third period of development (at least in the rat) there is evidence that the increase of single nephron GFR is largely related to increases in glomerular plasma flow (13). This suggests that filtration equilibrium may exist at this period, and consequently that although K_F is lower than in the adult, it is not responsible for the lower GFR. However, for filtration equilibrium to be maintained during development as renal plasma flow is increasing, K_F must also increase. Thus although the low K_F may not be responsible for the low GFR at this period of development, the maturational increase in K_F is necessary for the maturational increase in GFT. The increase in K_F is related largely to an increase in surface area of the glomerulus (21) but also perhaps to an increase in hydraulic conductivity (23). Although maturation of nephron GFR is primarily dependent on increases in renal plasma flow during the third period of development, it is likely that during the second (mid) developmental period, P_{GC} maturational increases play an important role. The relative importance of the low K_F on the one hand or the low GPF on the other during this period is not known and as mentioned previously will depend on the presence or absence of filtration equilibrium. In the early period, since there is little

Table 1
Developmental Periods of RBF and GFR Maturation

	Developmental Period		
	Early	Mid	Late
Animal model	Sheep fetus	Neonatal dog <10 wks Neonatal guinea pig Newborn lamb <2 mo Infant rat <40 days Newborn infant <4 mo	Infant rat >40 days Young dog Young lamb Infant human
Kidney growth	Nephrogenesis	Nephrogenesis (some species part of period)	Nephron maturation (some species part of period
	Nephron maturation Nephron growth	Nephron maturation Nephron growth	Nephron growth
Change in blood pressure	Slight increase	Large increase	Slight increase
RBF			
1) Total	Increase	Increase	Increase
2) Per kidney mass	Slight increase or no change	Increase	Slight or no change
3) Distribution	Toward outer cortex (slight)	Toward outer cortex	No change
RVR			
1) Total	Decrease	Decrease	Decrease
2) Per kidney mass	No change	Slight decrease or no change	Slight decrease or no change
Change in GFR			
1) Total	Increase	Increase	Increase
2) Per kidney mass	No change	Increase	No change
3) Single nephron	Slight increase or no change	Increase	Increase
P_{GC}	Slight increase or no	Increase	Slight increase or no change
GPF	Slight increase or no change	Increase	Increase
K_F	Increase	Increase	Increase

Developmental periods are arbitrary and vary from species to species. RBF, renal blood flow; GFR, glomerular filtration rate; RVR, renal vascular resistance; P_{GC}, glomerular capillary hydrostatic pressure; GPF, individual glomerular plasma flow; K_F, filtration coefficient.

change in GPF (29) and presumably therefore in single nephron GFR, the increase in total kidney GFR is probably due to the increasing number of nephrons.

Development of Renal Sodium Excretion

In the adult under control conditions more than 99% of the filtered sodium is reabsorbed by the tubules. Micropuncture studies reveal that about 70% of the filtered sodium is reabsorbed in the proximal tubule; the rest is reabsorbed more distally, largely in the ascending limb of the loop of Henle.

In the newborn dog and guinea pig the fractional reabsorption of water (and presumably sodium) at the end of the proximal tubule has been found to be relatively constant during maturation and similar to that for the adult (12, 33). In these animals the GFR increases as the animal matures; concomitantly, there is a proportional increase in proximal tubular sodium and water load and consequently in reabsorption. Similarly, in the newborn rat, as single-nephron GFR increases with maturation, proximal tubular sodium reabsorption increases proportionately (31). Although these studies might suggest that the development of tubular sodium reabsorption simply involves a proportional increase in reabsorptive capacity with that of glomerular filtered load, other experiments studying the maturation of the renal response to sodium loading reveal that the developmental pattern of tubular sodium reabsorption is somewhat more complex.

When an adult is given a large sodium load, there is an immediate expansion of the extracellular fluid space. This expansion stimulates the kidney to decrease tubular sodium reabsorption, resulting in increased excretion of sodium and a relatively rapid return of the extracellular fluid space to preload condition. When newborn infants and animals are given a sodium load, they experience a rise in serum sodium levels, abnormal increases in weight, and generalized edema (25). The poor renal response of the infant to the sodium load is due to its low GFR and its relatively high fractional tubular sodium reabsorption during the sodium loading. The ability to excrete the sodium load increases with age throughout the first year of life. This maturational increase in sodium excretion is due both to the increase in filtered sodium (due to maturational increase in the GFR) and to an increase in fractional sodium excretion (4).

Paradoxically, infants born prematurely before 36 wk gestation have a better sodium excretory response to sodium loading than do infants born later in gestation (3). As the premature infant matures over the first few weeks of life, its ability to excrete the sodium load declines rather than improves. Thus the developing kidney, in the human at least, seems to undergo a parabolic response to sodium loading; a slightly decreasing response with age early in development followed by an increasing response later in development.

The newborn dog has been used as a model for studying maturation of renal function, since its renal response to sodium loading is similar to that of the newborn infant. Newborn dogs excrete only 5% of a sodium load administered intravenously after 2 h, compared with 30% excretion of an equivalent load administered to adult dogs (20). The major reason for the difference in response is that the adult dog excretes 6–8% of the filtered sodium compared with only 1–2% excreted by the puppy (under nonexpanded conditions both adult and newborn dogs excrete about 0.2% of the filtered load). As can be seen from Fig. 5, over the first 3 wk of life there is no maturational change in the response to saline expansion in the dog (the slight decrease in response during the 2 wk was not statistically significant), but there is an increase in response beginning in the 4th wk. Thus the maturational pattern in the neonatal dog corresponds to that of the full-term human infant (or perhaps to that of the premature infant if the slight fall in response during the 2nd wk is indeed significant). Note that the maturational pattern of tubular response to saline expansion differs from that for intrarenal blood flow distribution (Fig. 2) and GFR (Fig. 4).

Elucidation of the mechanisms involved in maturation of sodium excretion during control and volume-expanded conditions can be obtained from results of experiments analyzing the tubular segmental locus of sodium reabsorption (Fig. 6). For the purpose of this discussion the kidney tubule is divided into two portions, proximal and distal. The proximal portion consists anatomically of the proximal convoluted tubule, the proximal straight tubule, and the descending limb of Henle's loop. The distal nephron consists of the ascending limb of Henle's loop, the distal convoluted tubule, and collecting ducts. Since micropuncture could not be done in animals at this age for reasons mentioned previously, these results were based on studies utilizing the distal blockade technique (10, 15, 16).

As can be seen from Fig. 6, in nonexpanded animals both the adult and newborn dog behave the same way. Approximately 70–75% of the filtered sodium is reabsorbed proximally while 20–25% is reabsorbed distally for a total reabsorption of greater than 99% of the filtered sodium. During saline expansion in the adult, proximal sodium reabsorption falls to about 60–65%, overall distal reabsorption changes little, and total reabsorption is about 92–94%; i.e., 6–8% of the filtered sodium is excreted. In the neonatal kidney, saline expansion results in a fall of proximal sodium reabsorption to less than 50%—a greater inhibition of sodium reabsorption than in the adult. However, the distal nephron reabsorbs more sodium than in the adult, so that in the end, a total of 98% of the filtered sodium is

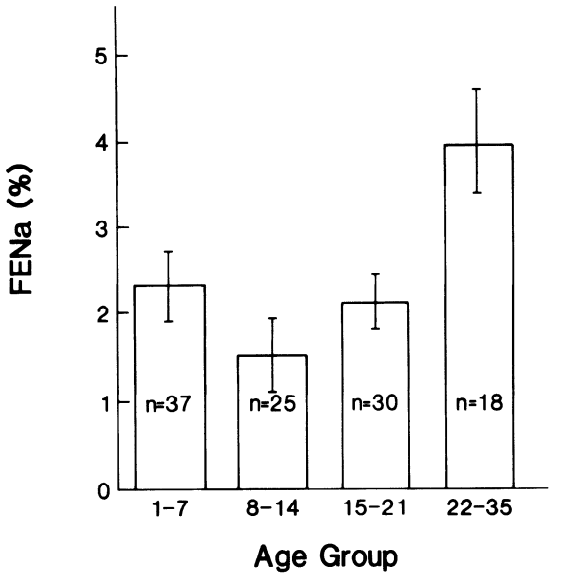


Figure 5
Maturation of fractional tubular sodium excretion in saline-expanded newborn dogs. [Based on data from various studies of the author (10, 15, 17)]

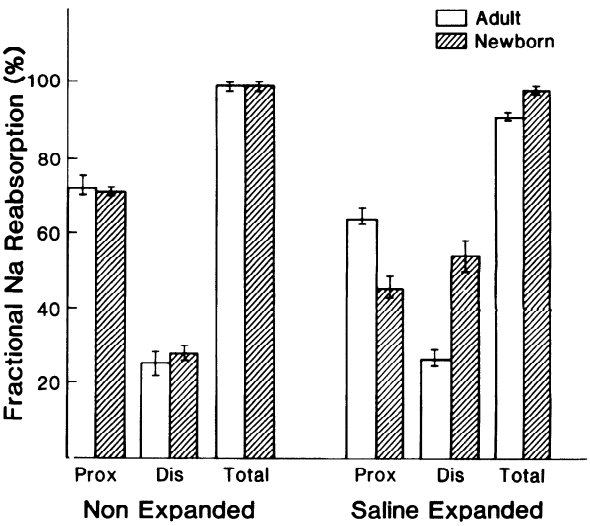


Figure 6
Fractional sodium reabsorption in proximal, distal, and total nephron during nonexpanded and saline-expanded states in newborn and adult dogs. [Based on data of Haramati and Kleinman (10) and Kleinman, Banks, and Disney (18)]

reabsorbed—greater than in the mature kidney. The major portion of this increased distal sodium reabsorption occurs in the loop of Henle. The reasons for the increased distal nephron sodium reabsorption in the developing kidney are still unclear and controversial and will not be discussed further in this paper.

Of particular interest are the findings in the proximal nephron in the dog. Without saline expansion fractional sodium reabsorption is the same in the adult and neonatal proximal tubule, but during saline expansion fractional sodium reabsorption is less in the neonatal proximal tubule kidney. These findings may be explained in terms of mechanisms of proximal tubule sodium reabsorption that include active sodium reabsorption, passive sodium reabsorption, and some degree of back

leak into the tubular lumen across the intercellular "tight" junction. Back leak across the tight junction is enhanced during volume expansion. There is some evidence of a "less tight" intercellular junction in the immature kidney (22). In addition, microperfusion studies of neonatal rabbit proximal tubules reveal increased leakiness compared with more mature tubules (11), and distal blockade studies reveal the proximal nephron of the newborn dog to be more susceptible to an osmotic diuresis than the adult (5), suggesting the greater propensity for back leak in the neonatal proximal tubule. This could explain the finding that under conditions of minimal back leak (nonexpansion) there is no or little difference in proximal tubular sodium reabsorption, whereas during extracellular volume expansion, which would enhance back leak, proximal sodium reabsorption is less in the immature than in the mature kidney.

A model of the maturational response to saline expansion is presented in Figs. 7 and 8. In the proximal tubule (Fig. 7) sodium load is continuously increasing during development due to the increase in GFR. Proximal tubule sodium reabsorption is also increasing (due both to an increase in active transport capacity and to a decrease in back leak). However, sodium reabsorption is increasing at a greater rate than the sodium load, so that the proximal sodium reabsorption divided by filtered load (fractional sodium reabsorption) continues to increase throughout periods 1–4. If the developmental increase in fractional sodium reabsorption during volume expansion is due largely to diminishing back leak, then it would not be apparent during nonexpansion and it would explain the finding of similar proximal fractional sodium reabsorption in newborn and adult animals during nonexpansion.

In the distal nephron sodium load (the amount of sodium not reabsorbed proximally) increases throughout the developmental period (Fig. 8) due to the increase in GFR, but it does not increase as much as the increase in load to the proximal tubule because of the maturational rise in proximal tubular sodium reabsorption. Distal sodium reabsorption increases continuously but at different rates than distal sodium loads. Thus from periods 1 to 2 the rate of increase of sodium reabsorption is greater than the rate of increase of distal sodium load, so that the ratio of sodium reabsorption to load (distal fractional sodium reabsorption) is increasing during this period. Since proximal fractional sodium reabsorption is also increasing (Fig. 7), overall frac-

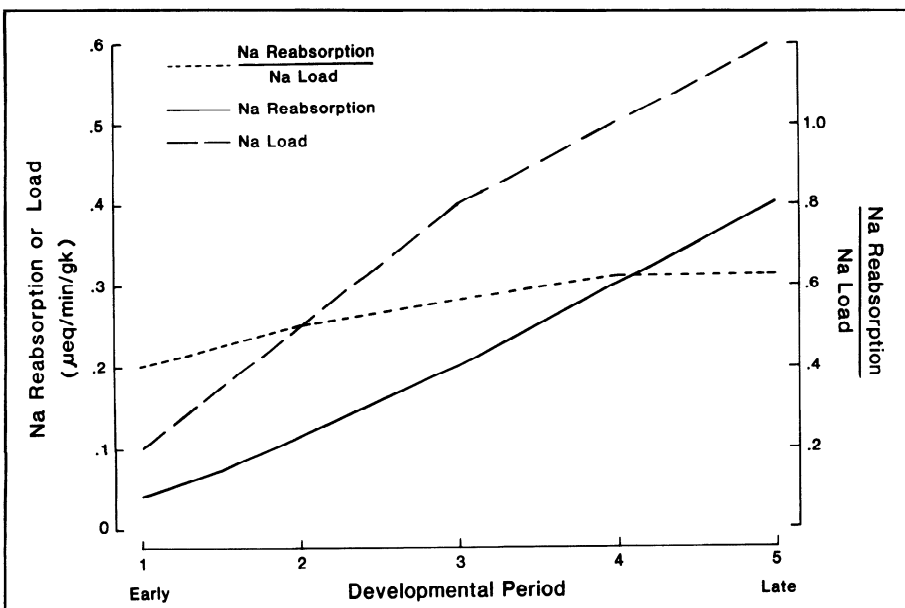


Figure 7
Maturational pattern of proximal sodium handling during saline expansion. Developmental periods are arbitrary and do not necessarily correspond to those described in Table 1.

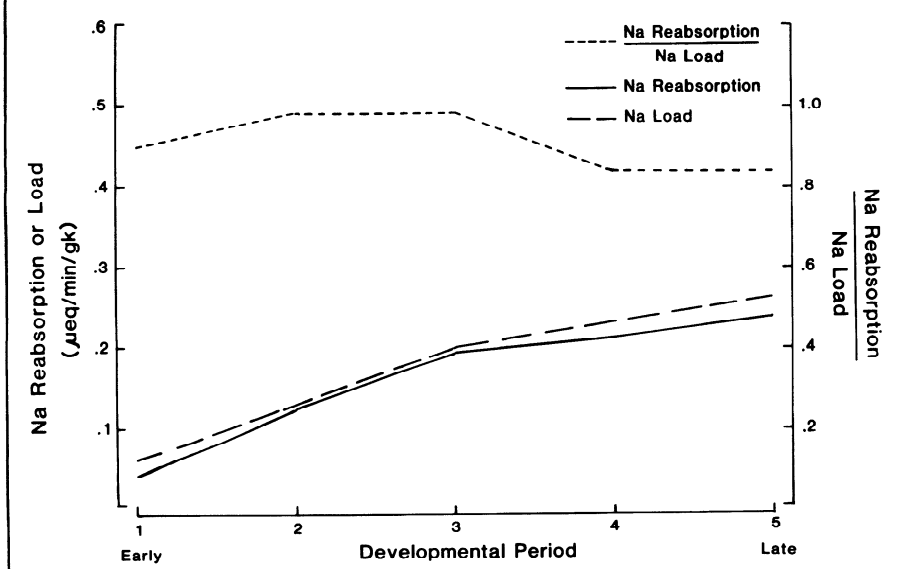


Figure 8
Maturational pattern of distal sodium handling during saline expansion. Developmental periods correspond to those described in Fig. 7.

tional sodium reabsorption is increasing and fractional sodium excretion is decreasing during this period. This would correspond to the developmental pattern in the premature infant when overall fractional sodium excretion is decreasing. During the next developmental period the rate of increase of distal sodium load equals that of distal sodium reabsorption; so there is no change in the ratio. From developmental periods 3 to 4 the rate of increase in distal sodium reabsorption is less than that of the sodium load, so that the ratio decreases to the mature level. However, this ratio falls at a greater rate than proximal fractional sodium reabsorption is increasing, so that overall fractional reabsorption decreases. This period corresponds to the maturational decrease in overall fractional sodium reabsorption seen in most animals. The model of development of proximal and distal sodium reabsorption capacity described above provides an explanation for the parabolic change in renal response to saline expansion in the human neonate and still allows for a continuous maturational increase in reabsorptive capacity for both proximal and distal tubules.

References

1. Allison, M.E.M., E.M. Lipham, and C.W. Gottschalk. Hydrostatic pressure in the rat kidney. *Am. J. Physiol.* 223: 975-983, 1972.

2. Aperia, A., O. Broberger, and P. Herin. Maturational changes in glomerular perfusion rate and glomerular filtration rate in lambs. *Pediatr. Res.* 8: 758-765, 1974.

3. Aperia, A., O. Broberger, K. Thodenius, and R. Zetterstrom. Developmental study of renal response to an oral salt load in preterm infants. *Acta Paediatr. Scand.* 63: 517-524, 1974.

4. Aperia, A., O. Broberger, K. Thodenius, and R. Zetterstrom. Development of renal control of sale and fluid homeostasis during the first year of life. *Acta Paediatr. Scand.* 64: 393-398, 1975.

5. Baker, J.T., and L.I. Kleinman. Relationship between glucose and sodium excretion in the newborn dog. *J. Physiol. London* 243: 45-61, 1974.

6. Behrman, R.E., and M.H. Lees. Organ blood flows of the fetal, newborn and adult rhesus monkey. *Biol. Neonate* 18: 330-340, 1971.

7. Friis, C. Postnatal development of renal function in piglets: glomerular filtration rate, clearance of PAH and PAH extraction. *Biol. Neonate* 35: 180-187, 1979.

8. Friis, C. Postnatal development of the pig kidney: ultrastructure of the glomerulus and the proximal tubule. *J. Anat.* 130: 513-526, 1980.

9. Gruskin, A.B., C.M. Edelmann, Jr., and S. Yuan. Maturational changes in renal blood flow in piglets. *Pediatr. Res.* 4: 7-13, 1970.

10. Haramati, A., and L.I. Kleinman. Chloride concentration gradient in newborn dogs in the presence of distal nephron blockade. *Am. J. Physiol.* 239 (*Renal Fluid Electrolyte Physiol.* 8) F328-F335, 1980.

11. Horster, M., and L. Larsson. Mechanisms of fluid absorption during proximal tubule development. *Kidney Int.* 10: 348-363, 1976.

12. Horster, M., and Valtin, H.: Postnatal development of renal function: micropuncture and clearance studies in the dog. *J. Clin. Invest.* 50: 779-795, 1971.

13. Ichikawa, I., D.A. Maddox, and B.M. Brenner, Maturational development of glomerular ultrafiltration in the rat. *Am. J. Physiol* 236 (*Renal Fluid Electrolyte Physiol.* 5): F465-F471, 1979.

14. Jose, P.A., L.M. Slotkoff, L.S. Lilienfield, P.L. Calcagno, and G.M. Eisner. Sensitivity of neonatal renal vasculature to epinephrine. *Am. J. Physiol.* 226: 796-799, 1974.

15. Kleinman, L.I. Renal sodium reabsorption during saline loading and distal blockade in newborn dogs. *Am. J. Physiol.* 228: 1403-1408, 1975.

16. Kleinman, L.I., and R.O. Banks. Natriuretic effect of oxytocin on saline expanded neonatal dogs. *Am. J. Physiol.* 239 (*Renal Fluid Electrolyte Physiol.* 8): F589-F594, 1980.

17. Kleinman, L.I., R.O. Banks, and T.A. Disney. Natriuretic effect of carotid occlusion in volume expanded newborn and adult dogs (Abstract). *Physiologist* 24(4): 11, 1981.

18. Kleinman, L.I., and R.J. Lubbe. Factors affecting the maturation of glomerular filtration rate and renal plasma flow in the newborn dog. *J. Physiol. London* 223: 395-409, 1972.

19. Kleinman, L.I., and J.H. Reuter. Maturation of glomerular blood flow distribution in the newborn dog. *J. Physiol. London* 228: 91-103, 1973.

20. Kleinman, L.I., and J.H. Reuter. Renal response of the newborn dog to a saline load: the role of intrarenal blood flow distribution. *J. Physiol. London* 239: 225-236, 1974.

21. Knutson, D.W., F. Chleu, C.M. Bennett, and R.J. Glassock. Estimation of relative glomerular capillary surface area in normal and hypertrophic rat kidneys. *Kidney Int.* 14: 437-443, 1978.

22. Larsson, L. Ultrastructure and permeability of intercellular contacts of developing proximal tubules in the rat kidney. *J. Ultrastruct. Res.* 52: 100-113, 1975.

23. Larsson, L., and A.B. Maunsbach. The ultrastructural development of the glomerular filtration barrier in the rat kidney: a morphometric analysis. *J. Ultrastruct. Res.* 72: 392-406, 1980.

24. MacDonald, M.S., and J.L. Emery. The late intrauterine and postnatal development of human renal glomeruli. *J. Anat.* 93: 331-340, 1959.

25. McCance, R.A., and E.M. Widdowson. Hypertonic expansion of the extracellular fluids. *Acta Paediatr. Scand.* 46: 337-353, 1957.

26. Potter, D., A. Jarrah, T. Sakai, J. Harrah, and M.A. Holliday. Character of function and size in kidney during normal growth of rats. *Pediatr. Res.* 3: 51-59, 1969.

27. Rankin, J.H.G., E.L. Gresham, F.C. Battaglia, E.L. Makowski, and G. Meschia. Measurement of fetal inulin clearance in a chronic sheep preparation. *J. Appl. Physiol.* 32: 129-133, 1972.

28. Robillard, J.E., C. Kulvinskas, C. Sessions, L. Burmeister, and F.G. Smith, Jr. Maturational changes in the fetal glomerular filtration rate. *Am. J. Obstet. Gynecol.* 122: 601-606, 1975.

29. Robillard, J.E., D.N. Weisman, and P. Herin. Ontogeny of single glomerular perfusion rate in fetal and newborn lambs. *Pediatr. Res.* 15: 1248-1255, 1981.

30. Rubin, M.F., E. Bruch, and M. Rappoport. Maturation of renal function in childhood: clearance studims. *J. Clin. Invest.* 28: 1144-1162, 1949.

31. Solomon, S. Absolute rates of sodium and potassium reabsorption by proximal tubule of immature rats. *Biol. Neonate* 25: 340-351. 1974.

32. Solomon, S. Developmental change in nephron number, proximal tubular length and superficial nephron glomerular filtration rate of rats. *J. Physiol. London* 573-589, 1977.

33. Spitzer, A., and M. Brandis. Functional and morphological maturation of the superficial nephrons and relationship to total kidney function. *J. Clin. Invest.* 53: 279-287, 1974.

A Block Diagram, Graphical and Microcomputer Analysis of the O_2 Transport System

DAVID A. MILLER AND WESLEY M. GRANGER
Department of Physiology
Medical College of Georgia
Augusta, Georgia 30912

MILLER, DAVID A., and WESLEY M. GRANGER. A Block Diagram, Graphical and Microcomputer Analysis of the O_2 Transport System. *Physiologist* (25(2): 000-000, 1982.—The systematic description of O_2 transport from the ambient air to the tissues involves a variety of environmental, pulmonary, heart, tissue, and blood parameters. Using essentially the law of conservation of mass and the total blood O_2 content vs. O_2 partial pressure (P_{O_2}) relationship, the variables and parameters of O_2 transport can be related in the form of a block diagram. This system block diagram has proved useful to examine factors that influence O_2 transport. A mathematical description of the system has been programmed on an Apple II microcomputer. The computer can be used to predict the relationship between alveolar, arterial, and mixed venous P_{O_2} and any given system parameter. To augment our understanding of some of the more complex findings, we developed a graphical analysis that involves manipulation on the total O_2 content vs. P_{O_2} diagram. Even though the graphical technique is less exact than the computer, it provides better insight into the characteristic features of a given result. This technique reinforces the understanding of the equations used in the block diagram and provides an in-hand method for determining the effect of any system parameter on the alveolar, arterial, or mixed venous P_{O_2}.

The transport of O_2 from ambient air to the tissue is affected by a variety of environmental, lung, heart, tissue, and blood parameters. Because of the large number of parameters and relationships involved in this system, its analysis or understanding often cannot be dealt with adequately using word arguments or singular aspects (e.g., the O_2 dissociation curve) of the total system. An inadequate analysis can result in wrong answers or possibly right answers for the wrong reasons. For example, if a patient has a lowered arterial O_2 partial pressure ($Pa_{O_2} = 60$ mmHg) and a low hemoglobin concentration (hb = 10 g/100 ml), is the low Pa_{O_2} accounted for entirely by the low Hb? The answer is not a simple yes or no, since it depends on the adequacy of gas exchange. With normal gas exchange low Hb does not appreciably affect Pa_{O_2}, whereas with impaired gas exchange it can significantly influence the Pa_{O_2}. This example illustrates the complex behavior possible in the O_2 transport system. The importance of interpreting various blood gas measurements (e.g. arterial and mixed venous P_{O_2}) is underscored by their widespread use in various medical specialties and the potential critical nature of abnormal values.

In this paper a systematic description and block diagram for O_2 transport is developed that allows a rigorous interpretation of important clinical variables such as the alveolar, arterial, and mixed venous P_{O_2} (PA_{O_2}, Pa_{O_2}, and $P\bar{v}_{O_2}$, respectively) and the alveolar CO_2 partial pressure (PA_{CO_2}). In addition, a graphical analysis is developed using a total O_2 content vs. P_{O_2} graph so that the total system can be treated. The graphical analysis supplements the block diagram and provides a method to determine the effect of any system parameter [Hb concentration, pH, cardiac output ($\dot{Q}T$)] on the clinical variable of interest. This material and presentation has been used for 2 years in a medical physiology course.

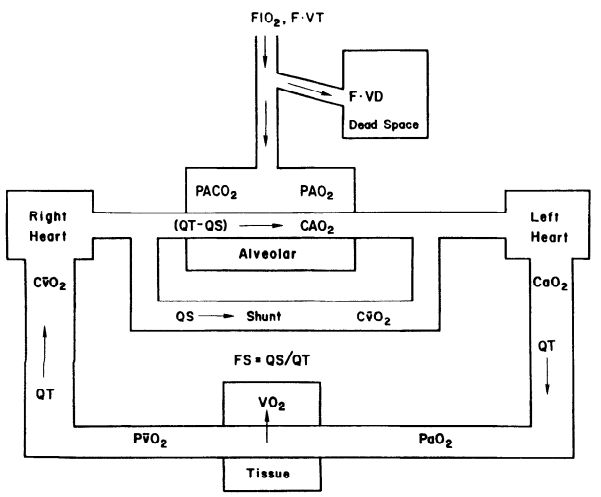
The block diagram is an excellent integrating tool for the material developed early in the respiratory physiology section including the gas laws, mechanics, gas exchange, and transport. Later respiratory control mechanisms are easily discussed in terms of the foundation established by the block diagram. A laboratory session is used to introduce the microcomputer system to the students. Several demonstration exercises and clinical cases are discussed in this laboratory session. This session gives the students the opportunity to try therapeutic measures that they have either read or heard about.

System Description

The O_2 transport system has been formulated on the basis of the conventional three-compartmental model for pulmonary gas exchange (4) that includes dead-space, alveolar and shunt compartments and a tissue compartment that utilizes O_2 (Fig. 1). Since this is a steady state model tissue O_2 utilization is assumed to be equal to O_2 uptake at the lungs. The transport of O_2 to the gas exchange region is dependent on the tidal volume (VT), breathing frequency (F), and the inspired fraction of O_2 (FI_{O_2}). The dead-space compartment is represented by a dead-space volume, which is the portion of the VT that does not reach perfused alveoli. Thus for this portion of the breath no gas exchange occurs, and consequently the effective ventilation is reduced particularly when this volume is large. The volume of the conducting airways normally accounts for the major portion of the dead-space volume. Examples of increased dead-space volume would include breathing through a tube or pulmonary emboli that block perfusion to ventilated areas. The alveolar compartment is represented by a gas exchange space that is both ventilated and perfused. In this compartment it is assumed that the blood comes into perfect equilibrium with the alveolar gas concentrations. The shunt compartment is represented by a shunt flow ($\dot{Q}S$), which is the portion of the venous return that would have to be added to the arterial blood to account for the difference between the O_2 arterial content (Ca_{O_2}) and the O_2 content of the blood equilibrated with the alveolar space (CA_{O_2}).[1] $\dot{Q}S$ divided by $\dot{Q}T$ yields the shunt fraction (FS), which is a quantitative measure of an O_2 exchange abnormality

[1]This O_2 content has conventionally been referred to as pulmonary end-capillary O_2 content[2] and designated C'_{O_2}; however, we feel that the designation CA_{O_2} more appropriately connotes the true nature of this variable.

Figure 1
O_2 transport compartmental model.



(3). However, the FS does not specify the abnormality. An increased FS can indicate *1*) an anatomical shunting of blood that bypasses the alveolar space (e.g., atelectasis), *2*) a diffusion abnormality, *3*) a ventilation-perfusion abnormality, or *4*) some combination of the above.

O_2 Transport Block Diagram

Conventional equations and relationships (6) are available to describe the above compartments of the O_2 transport system and include *1*) the alveolar gas equation, *2*) the definition of a dry gas fraction, *3*) total O_2 content vs P_{O_2} diagram, *4*) FS equation, and *5*) Fick's principle. Each of these five relationships can be expressed in several forms. The form utilized in our analysis allows each new variable to be expressed in terms of the previously introduced variable and one or more system parameters (Fig. 2). In this way the dependency of any variable can be determined by observing the variables or parameters that appear in a previous block. In addition, variables and parameters are introduced at a level that is most consistent with their structural or functional appearance in the system.

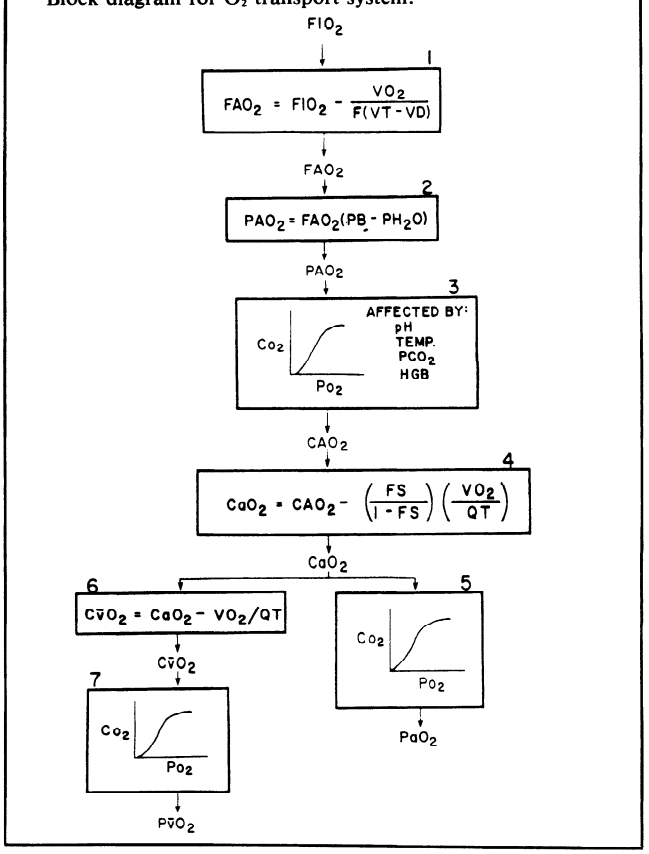
The system block diagram provides an orderly and logical way to view the relationships of the O_2 transport system. Accordingly, the beginning point in the diagram is $F_{I_{O_2}}$, which is a frequently manipulated parameter during O_2 therapy. In block 1, the alveolar gas equation is used to express the alveolar fraction of O_2 ($F_{A_{O_2}}$) as a function of the $F_{I_{O_2}}$, O_2 consumption ($\dot{V}O_2$), and the ventilatory parameters, F, VT, and the physiological dead-space volume (VD). Alveolar ventilation ($\dot{V}A$) is given by F(VT − VD). In block 2, FAO_2 is converted to $P_{A_{O_2}}$ by utilizing the definition of a dry gas fraction. $P_{A_{O_2}}$ is expressed as a function of the barometric pressure (PB) and the partial pressure of water vapor (P_{H_2O}). PB is altered in diving and at altitude, and P_{H_2O} varies with temperature. Since there can be variation of local $P_{A_{O_2}}$ across the lung due to local diffusion or ventilation-perfusion differences, $F_{A_{O_2}}$ and $P_{A_{O_2}}$ should be viewed as compartmental values consistent with $\dot{V}A$ and $\dot{V}O_2$. Block 3 represents the relationship between total O_2 content (dissolved + Hb carriage) of the blood and its P_{O_2}. This relationship is influenced by blood pH, temperature, and P_{CO_2}. Although 2,3-diphosphoglycerate can also influence the curve, its concentration is assumed to remain constant in the model, because clinical data on this parameter are generally not available. The blood that perfuses the alveolar compartment is assumed to reach perfect equilibrium with the alveolar gases. Therefore, the total O_2 content of that blood has been designated $C_{A_{O_2}}$. In block 4, the total $C_{a_{O_2}}$ is calculated using a combined form of the FS equation and Fick's principle. For normal values of FS (0.02), $C_{a_{O_2}}$ will approach $C_{A_{O_2}}$; however, when FS increases their difference will increase and also be influenced by $\dot{V}O_2$ and $\dot{Q}T$. In block 5, working backward through the total O_2 content vs. P_{O_2} graph will yield one of the desired variables, $P_{a_{O_2}}$. This variable is heavily relied on as a clinical index of the general state of oxygenation of the individual. In block 6, the mixed venous O_2 content ($C\bar{v}_{O_2}$) can be obtained from $C_{a_{O_2}}$ and parameter values by using Fick's principle. In block 7, $P\bar{v}_{O_2}$ can be obtained from $C\bar{v}_{O_2}$ via the total O_2 content vs. P_{O_2} graph. $P\bar{v}_{O_2}$ is used clinically as an index of tissue oxygenation.

$P_{A_{CO_2}}$ can also be calculated from $F_{A_{CO_2}}$

$$P_{A_{CO_2}} = F_{A_{CO_2}}(PB - P_{H_2O}) \qquad (1)$$

where $F_{A_{CO_2}} = \dot{V}CO_2/\dot{V}A$. CO_2 production ($\dot{V}CO_2$) is obtained from $R \cdot \dot{V}O_2$, where R, the respiratory exchange ratio, is assumed to be equal to 0.8 and all gas volumes are measured under BTPS conditions. $\dot{V}A$ is calculated from $F \cdot (VT - VD)$. Since $P_{A_{CO_2}}$ is determined from a fixed relationship (Eq. 1) with other system parameters (R, $\dot{V}O_2$, F, VT, VD, PB, P_{H_2O}), it is not input separately as a parameter. Alveolar, arterial, and mixed venous

Figure 2
Block diagram for O_2 transport system.



P_{CO_2} ($P_{A_{CO_2}}$, $P_{a_{CO_2}}$, and $P_{\bar{v}_{CO_2}}$, respectively) are assumed equal for the calculations involving the total O_2 content vs. P_{O_2} graph.

Since pH is related to P_{CO_2}, one might consider calculating pH also. However, this relationship is very complex. For example, in respiratory and metabolic disturbances, there is not a fixed relationship between the two variables. Even in a respiratory disturbance alone, such a hyperventilation, the relationship between pH and P_{CO_2} can vary with time and Hb. Thus, because of the complexity involved, pH is not calculated from P_{CO_2} in the computer program but must be input separately. Arterial and mixed venous pH are also assumed equal for calculations involving the total O_2 content vs. P_{O_2} graph. Since the P_{H_2O} is determined solely by the temperature, it is calculated in the computer program from the input value of temperature.

With the systematic description complete, it is of interest to examine the various system parameters to determine what anatomical or functional components they represent. Table 1 indicates that a variety of organs influence the behavior of the O_2 transport system, and it is this spectrum of components that must be initially considered in abnormal states as opposed to immediately focusing on the lungs or heart. As such, the initial clinical assessment should be to establish the abnormal anatomical or functional component so that some appropriate therapeutic regimen can be implemented. Table 2 shows the normal values that have been used for the system parameters and variables along with some of the typical conditions or influences that might change the parameter values.

The block diagram has proved to be extremely useful for answering very basic questions that students have had about the O_2 transport system. For example,

1) What are all the parameters that affect $P_{a_{O_2}}$? This question is esily answered by just listing all the parameters that appear above $P_{a_{O_2}}$ in the block diagram, since each of these parameters would influence the calculation of $P_{a_{O_2}}$. This list would also include the parameters that affect the total O_2 content vs. P_{O_2} graph.

2) What parameters affect the arteriovenous O_2 content difference? Small rearrangement of block 6 shows that this difference is only influenced by $\dot{V}_{O_2}$ and $\dot{Q}_T$.

3) With normal gas exchange (FS = 0.02), why does $\dot{V}_{O_2}$ have a large effect on $P_{a_{O_2}}$ and $\dot{Q}_T$ does not? The effect of $\dot{V}_{O_2}$ and $\dot{Q}_T$ on $C_{a_{O_2}}$ in block 4 of the block diagram is modified by the factor FS/(1 − FS). When FS is small (normal = 0.02), it minimizes the influence of $\dot{V}_{O_2}$ and $\dot{Q}_T$ on $C_{a_{O_2}}$ in block 4. However, $\dot{V}_{O_2}$ also appears in block 1 of the diagram and has a major influence on $P_{A_{O_2}}$ and $C_{A_{O_2}}$ only in block 4 and therefore has a minimal influence when FS is small.

Graphical Analysis

In our efforts to examine and to understand the system, we developed a graphical analysis that utilizes the total O_2 content vs. P_{O_2} relationship. All of the system relationships of Fig. 2 can be taken into account using this graphical technique. Therefore the effect of perturbing any system parameter can be examined. The total O_2 content vs. P_{O_2} graph is shown in Fig. 3. The entry point on the graph is $P_{A_{O_2}}$, which can be calculated from the equation designated as (*1*) in Fig. 3.

Table 1
Parameters of O_2 Transport System

Parameter	Anatomical of Functional Component
F	Respiratory center, central and peripheral respiratory receptors
VT	Respiratory center, central and peripheral respiratory receptors, respiratory muscles and elastic properties of the lungs and chest wall
V_D, FS	Lungs
$\dot{Q}_T$	Heart
$\dot{V}_{O_2}$	Body tissues
Hb, pH, P_{CO_2}, temperature	Blood
F_{IO_2}, P_{H_2O}, P_B	Environment

Table 2
Normal Values and Disturbances to System Parameters and Variables

Parameter	Altered by Condition or Influence
$\dot{V}_{O_2} = 250$ ml/min	Temperature (↑ 1°F → 7% $\dot{V}_{O_2}$ ↑), abnormal thyroid function
$\dot{V}_{CO_2} = 200$ ml/min	Related to $\dot{V}_{O_2}$ by R
$R = \dot{V}_{CO_2}/\dot{V}_{O_2} = 0.80$	Substrate for Metabolism (fat, protein, or carbohydrate)
$V_D = 150$ ml/breath	Pulmonary embolus
FS = 0.02	Diffusion abnormalities, ventilation-perfusion maldistribution, anatomical shunts (bronchail veins, Thebesian veins), alveolar shunts (collapsed alveoli)
$\dot{Q}_T = 5.0$ l/min	Blood volume, sympathetic system, drugs
$F_{IO_2} = 0.21$	O_2 therapy
$P_{H_2O} = 47$ mmHg	Temperature
$P_B = 760$ mmHg	Altitude or diving
Hb = 15 g/100 ml	Polycythemia, anemia
Temperature = 37 °C	Fever, drugs, environment
pH = 7.40	Metabolic or respiratory acid-base disturbance
F = 10 breaths/min	Disturbance of respiratory center or receptors
$V_T = 500$ ml/breath	Disturbances of respiratory center or receptors, abnormal chest or lung compliance, or abnormal respiratory muscle function

Normal Values for Variables

$P_{A_{O_2}} = 100$ mmHg	$P_{A_{CO_2}} = 40$ mmHg
$P_{a_{O_2}} = 94$ mmHg	$C_{A_{O_2}} = 20.6$ vol%
$P_{\bar{v}_{O_2}} = 40$ mmHg	$C_{a_{O_2}} = 20.5$ vol%
$P_{a_{CO_2}} = 40$ mmHg	$C_{\bar{v}_{O_2}} = 15.5$ vol%

This is a combined form of blocks 1 and 2 in Fig. 2. Knowing $P_{A_{O_2}}$, $C_{A_{O_2}}$ is obtained graphically in Fig. 3 (see arrows). Knowing $C_{A_{O_2}}$ and the parameters of the equation designated as (*2*) in Fig. 3, $C_{a_{O_2}}$ is calculated. This value is used on the graph (see arrows) to obtain $P_{a_{O_2}}$, which is an important clinical variable. Knowing $C_{a_{O_2}}$, and the parameters of the equation designated as (*3*) in Fig. 3, $C_{\bar{v}_{O_2}}$ is calculated; from this $P_{\bar{v}_{O_2}}$ is obtained graphically.

Figures 4-6 show how this basic graphical analysis can be used to determine the effects of parameter variations on $P_{A_{O_2}}$, $P_{a_{O_2}}$, and $P_{\bar{v}_{O_2}}$. In Fig. 4, the effect of two different concentrations of Hb is examined. The curves relating P_{O_2} and total O_2 content are shown for Hb concentrations of 15 and 7.5 g/100 ml. Variables associated with the lower Hb are denoted by a prime. $P_{A_{O_2}}$, which is the entry point on the graph, is the same

Figure 3
Graphical analysis of O_2 transport.

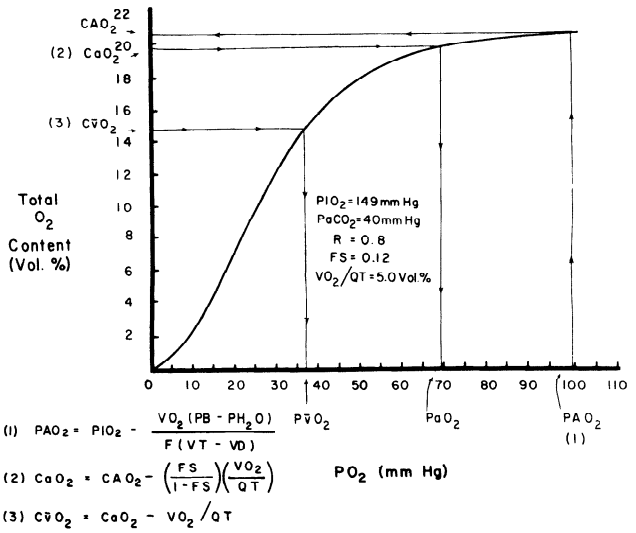


Figure 4
Graphical analysis of effect of hemoglobin concentration on O_2 transport.

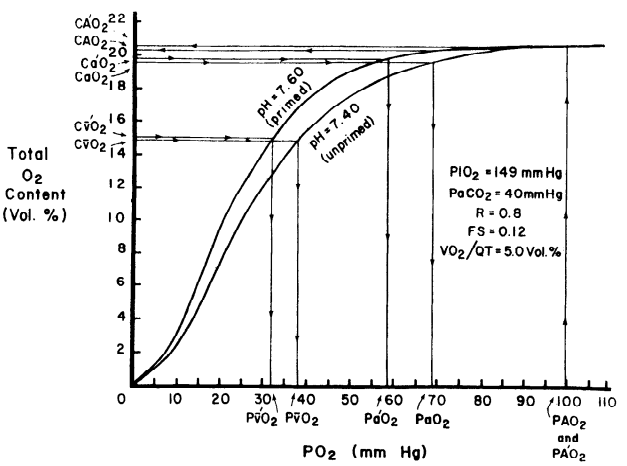


Figure 5
Graphical analysis of effect of pH on O_2 transport.

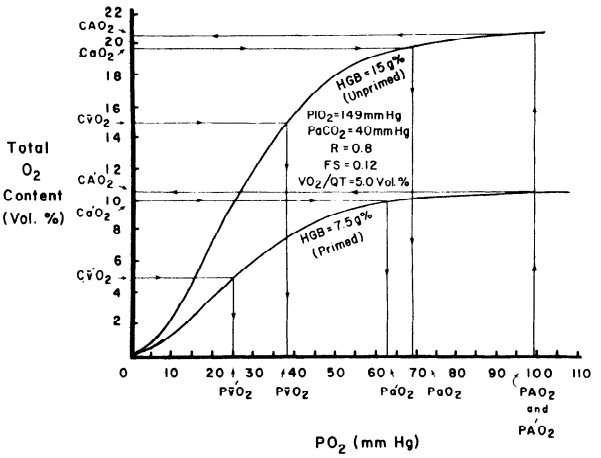
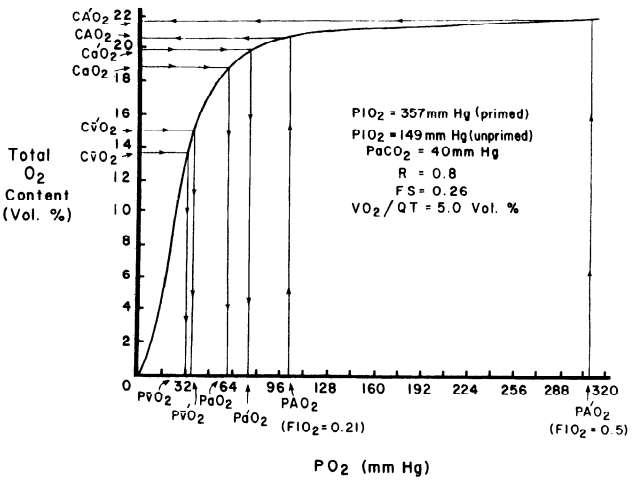


Figure 6
Graphical analysis of effect of fraction of inspired O_2 on O_2 transport.



for both cases because this variable is unaffected by Hb. The values for CA_{O_2} and $C'A_{O_2}$ are obtained from the appropriate curve. Next Ca_{O_2} and $C'a_{O_2}$ are calculated from the alveolar O_2 contents and parameter values and then used graphically to determine Pa_{O_2} and $P'a_{O_2}$. Then $C\bar{v}_{O_2}$ and $C'\bar{v}_{O_2}$ are calculated from arterial O_2 contents and parameter values and used graphically to determine $P\bar{v}_{O_2}$ and $P'\bar{v}_{O_2}$. These results can now be used to evaluate the effects of Hb. For this set of parameter values the largest influence of Hb is on $P\bar{v}_{O_2}$.

In Fig. 5 the effect of pH on O_2 tensions and contents is evaluated in a manner identical to that used for Hb. For the set of parameter values used, pH is shown to alter both arterial and mixed venous O_2 tensions.

The effect of FI_{O_2} on O_2 transport is evaluated in Fig. 6. Since changing FI_{O_2} alters PA_{O_2}, the entry points on the graph are different. The influence of FI_{O_2} on the arterial tension will be highly dependent on FS, which affects the vicinity in which the arterial content falls. This in turn can markedly alter the arterial tension in the saturation region of the curve. Since $C\bar{v}_{O_2}$ will usually fall on the steep portion of the graph, mixed venous tensions are affected by FI_{O_2} in a similar way for most sets of parameter values.

Figures 4–6 illustrate the use of the graphical technique for evaluating the effects of Hb, pH, and FI_{O_2} on O_2 transport. In a similar fashion, the effect of any other system parameter could be evaluated.

The graphical analysis has been particularly useful in helping students understand the following difficult points about O_2 transport behavior.

1) With abnormal gas exchange (large FS) Pa_{O_2} is significantly influenced by Hb or $\dot{Q}T$, whereas with normal gas exchange (small FS) it is not. It is imperative to understand the complex behavior of Pa_{O_2}, since this is a frequently measured and highly relied upon clinical variable.

2) Some disturbances (i.e., ↑ CO, ↓ $\dot{Q}T$, ↑ pH, ↓ temperature, and ↓ Hb) decrease $P\bar{v}_{O_2}$ without significantly affecting Pa_{O_2}. The recognition and understanding of these disturbances is important, because in these cases tissue hypoxia that is undetectable by observing Pa_{O_2} is occurring.

3) The clinical index ($PA_{O_2} - Pa_{O_2}$) for gas exchange is extremely sensitive to FI_{O_2} and ($Ca_{O_2} - C\bar{v}_{O_2}$) as well as the gas exchange function (FS). Understanding the factors that influence this difference allow better utility of it as an index.

The above behaviors as well as many others are readily understood by using the graphical analysis. In addition the graphical analysis has seemed to help the students gain confidence in using the microcomputer program, since they know they have a tool they can fall back on to explain the results.

Microcomputer Analysis

The O_2 model has been programmed on an Apple II microcomputer with graphics. The computer graphics plots $P_{A_{O_2}}$, $P_{a_{O_2}}$, $P_{\bar{v}_{O_2}}$, and $P_{A_{CO_2}}$ on the *Y*-axis. The user can choose the parameter to be changed systematically on the *X*-axis and then either keep the normal values for the other parameters or enter known values. In this mode the effect of each parameter on the O_2 transport variables can be examined. The graphics that appear on the screen in this mode are shown in Fig. 7. In this example the effect of the parameter $\dot{Q}_T$ on the O_2 transport variables is shown.

Another program choice is the comparison mode, which allows examination of the effect of a single parameter change and then the additional effects that may result from concomitant parameter or variable changes. For example, $\dot{V}_{O_2}$ increases when body temperature increases, and V_T and F are altered by arterial pH, P_{CO_2}, and P_{O_2}. Thus parameter and variable interdependence can be examined in the comparison mode in a stepwise manner that facilitates the understanding of the effects of the initial disturbance and the physical changes or physiological responses that accompany it. The comparison mode has also been used to demonstrate to the students unusual system behavior. One example is a change in conditions that causes $P_{a_{O_2}}$ and $P_{\bar{v}_{O_2}}$ to change in opposite directions. Figure 8 shows the comparison-mode graphics that appear for the conditions $\dot{Q}_T$ = 6.0 l/min and F_S = 0.3 (designated as 1st) and for the conditions $\dot{Q}_T$ = 3.0 l/min and F_S = 0.1 (designated as 2nd). This particular demonstration generally stimulates the student to return to the graphical analysis and block diagram to explain this result and also drives home the point that a logical and orderly approach is necessary to understand the O_2 transport system.

Figure 7
Microcomputer graphics showing effect of cardiac output on O_2 transport variables.

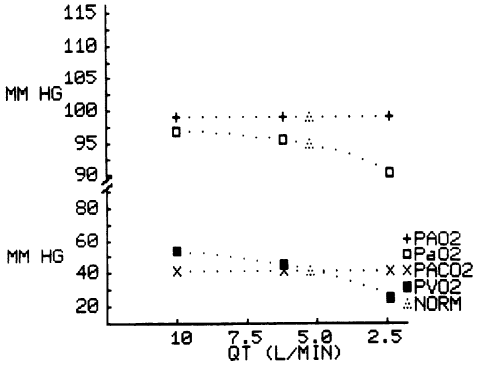
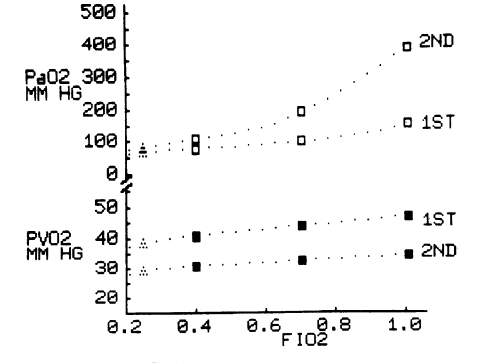


Figure 8
Microcomputer graphics in comparison mode (see text for explanation).



The following are notes about the O_2 transport computer program. The program has been written in Applesoft BASIC and can be run on a 48-K Apple II system with an Applesoft BASIC language card.

1) The disk operating system (DOS 3.3) has been programmed so that when the computer is turned on, the system will automatically begin to run the O_2 transport program. Thus, after turning the computer on, the user needs only to follow the instructions on the screen.

2) Acceptable ranges for parameter values have been programmed into the computer. If a parameter value is entered that is not within the acceptable range, the program will continue to ask for reentry of the parameter.

3) The O_2 transport system has been programmed to automatically scale the *Y*-axis so that maximal utilization of the screen is obtained.

4) The O_2 saturation curve used in this model is that of Gomez (1). The corrections for pH, temperature, and P_{CO_2} are those used by Kelman (2). The equation used to calculate P_{H_2O} from temperature is from Siegel (5).

5) Since the original program was too long to run without erasing the graphics page of memory, a utility program was applied to the Applesoft BASIC program to reduce it in length. A listing of this reduced program is unreadable, since all of the internal documentation has been eliminated. A flowchart of the computer program is given in Figs. A1 and A2 of the Appendix. A diskette copy, which includes the symbols table and character generator (both in binary) and additional documentation of the program, is available by sending a blank diskette to Wesley M. Granger, Dept. of Physiology, Medical College of Georgia, Augusta, GA 30912.

In conclusion, this presentation is viewed as an elementary but fundamental teaching package for O_2 transport. The block diagram allows a logical and orderly examination of influences that act on one or more parts of the system. The graphical analysis provides a visual operational tool to predict the magnitude and direction of these influences. The microcomputer program with graphics facilitates the examination of the system and provides ready access to correct responses.

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References

1. Gomez, D.M. Considerations of oxygen-hemoglobin equilibrium in the physiological state. *Am. J. Physiol.* 200: 135-142, 1961.

2. Kelman, G.R. Digital computer subroutine for the conversion of oxygen tension into saturation. *J. Appl. Physiol.* 21: 1375-1376, 1966.

3. Nunn, J.F. *Applied Respiratory Physiology.* Boston, MA: Buttersworths, 1978, p. 277-298.

4. Riley, R.L., and A. Cournand. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J. Appl. Physiol.* 1: 825, 1949.

5. Siegel, D. An improved program to calculate intrapulmonary shunting. *Crit. Care Med.* 7: 282-284, 1979.

6. West, J.B. *Respiratory Physiology—The Essentials.* Baltimore, MD: Williams & Wilkins, 1979.

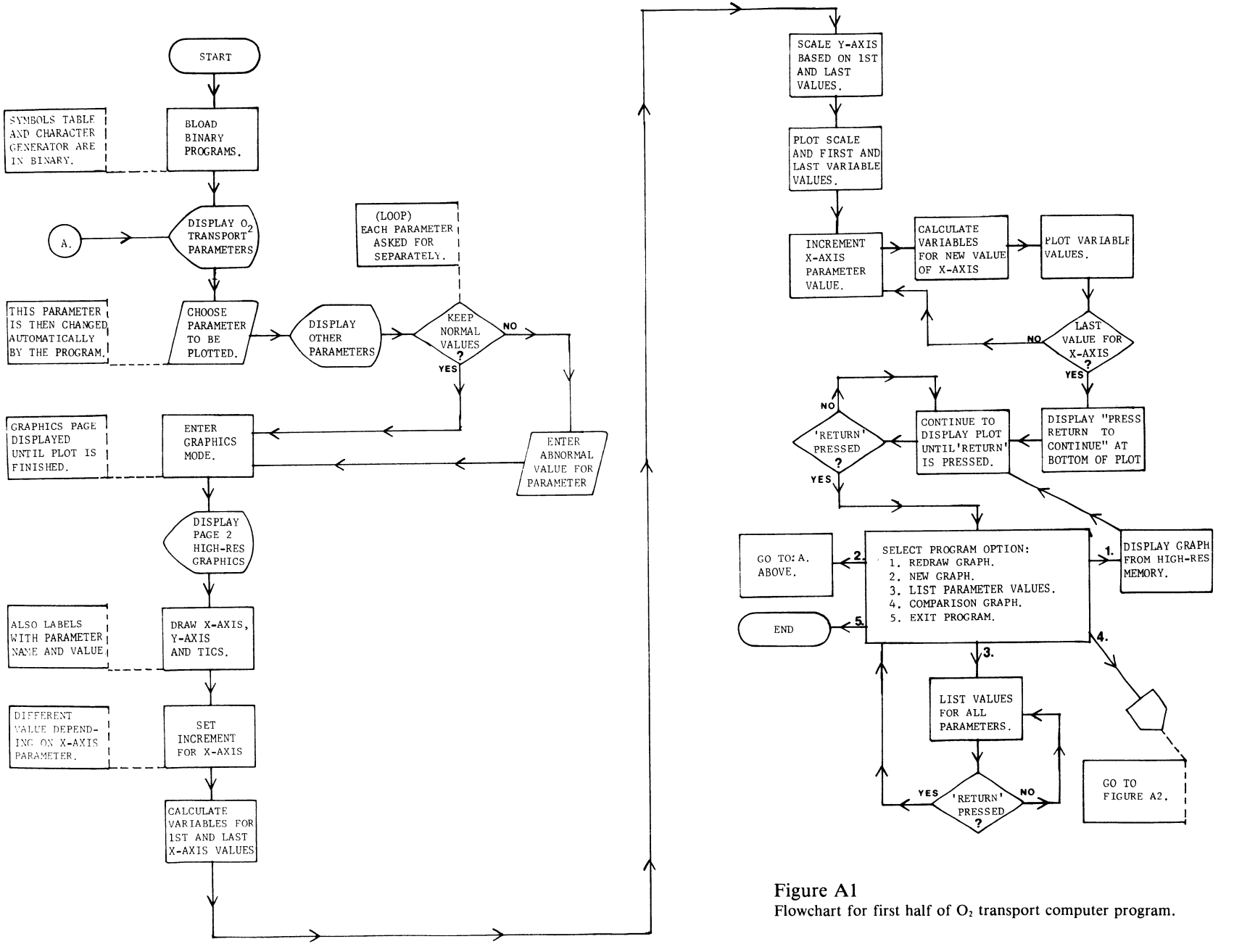

Figure A1
Flowchart for first half of O_2 transport computer program.

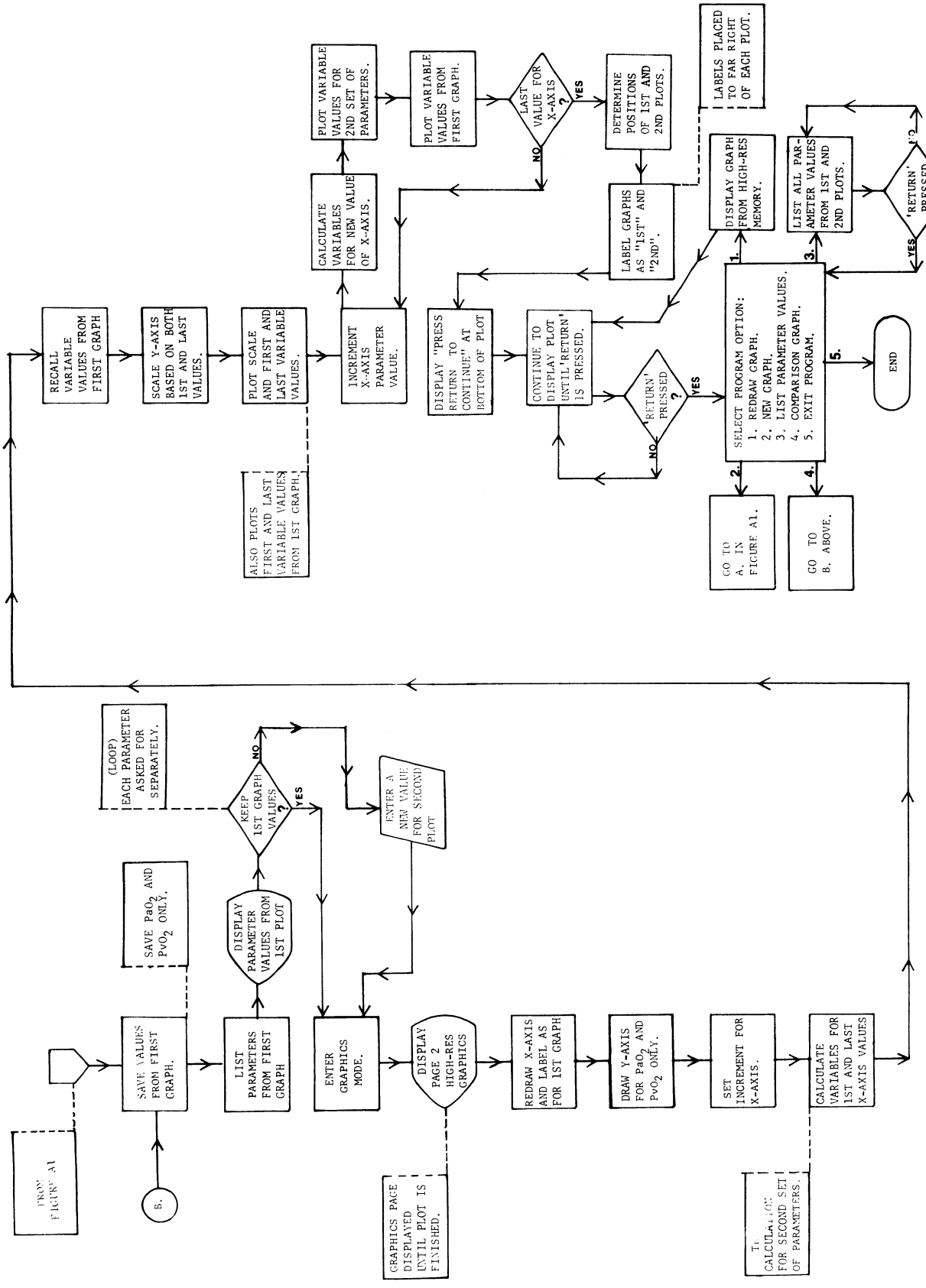

Figure A2
Flowchart for second half of O_2 transport computer program.

Teaching the Physiology of Aging in Undergraduate Medical Education

J. A. SPITZER
Department of Physiology and Medicine
Louisiana State University Medical Center
New Orleans, Louisiana 70112

The explosive rise in average life expectancy during this century and the virtually exponential increase in the number of older people, as well as the percentage of the total population made up by the elderly, create unprecedented problems for every practicing physician and for students about to embark on a career in medicine.

Aging is a universal process from which no one, if living long enough, is exempt. Furthermore, senescence is not an acute illness, but a long drawn-out condition of successive changes and adaptations. It is of great pragmatic importance for the practicing physician (especially the family-care practitioner or internist) to be aware of physiological changes due to the aging process, since his/her practice is likely to include in increasing proportions persons past their young adulthood. One of the major challenges facing medical education today is to address this problem properly.

It is imperative that medical education programs design means to provide a fundamental knowledge base from which new health services can be developed. In conjunction with the biomedical scientific perspective, emphasis has to be placed on special clinical skills to make possible fresh insights into the understanding, diagnosis, and management of clinical syndromes associated with advancing age.

As a practical suggestion, I would like to present for consideration the incorporation into medical school curricula of an elective course in Geriatric Physiology/Medicine, geared to about 20 first-year medical students. The *objectives* of such a course would be *1)* correlation of the scientific foundation of major geriatric problems with clinical manifestations and management strategy; and *2)* acquisition of basic and clinical knowledge, skills, and attitudes to better understand and treat geriatric illnesses in the context of medical and psychosocial determinants of disease. The *didactic* part of the course would consist of 1 hour per week lectures and/or conferences. Within the *practical* portion of the course, each student would be assigned to follow the care and progress of a selected patient, possibly in a chronic-care facility. Students would be required to spend at least 1 hour per week for a minimum of 6 months with their patient. Such a setting would provide opportunities for developing interviewing skills, learning to conduct a thorough physical examination, and acquiring knowledge of evaluating clinical laboratory data.

In the lecture/conference format, age-related changes of the following psysiological functions or systems could be discussed: vision, auditory function, locomotor system, cardiovascular system, pulmonary function, renal function, metabolic changes (carbohydrate and lipid metabolism), immunologic competence, peripheral and central nervous system, and bone loss.

Clinical correlation lectures could be integrated with each presentation of physiological alterations brought about by senescence. Clinical manifestations and some resultant geriatric problems to be discussed would include atherosclerosis (cerebral syndromes, confusion), cerebrovascular accidents, peripheral vascular disease, osteoporosis and osteoarthritis (falls, fractures), anemia, electrolyte and body fluid disorders (drug tolerance and interaction), diabetes, infections (pressure sores), alimentary disorders (nutritional problems, undernutrition), sensory problems (blindness and deafness), incontinence, cancer, and senile dementia of the Alzheimer type.

The general overview of such a course would integrate the physiological decline due to aging with increased incidence of age-related diseases, as well as the reduced ability to respond to challenges, precipitating increasingly deleterious consequences of disease with advancing age.

Biology of Aging

EDWARD J. MASORO
Department of Physiology
The University of Texas Heath
Science Center at San Antonio

The Department of Physiology presents an elective course in the biology of aging for graduate students in biomedical sciences and for senior medical students. The major reason for this elective is that neither group has much exposure to biological gerontology during their training. Other reasons are the rapidly growing population of aged people in our nation who require medical care from knowledgeable health professionals and the increasing opportunities for biologists to engage in aging research. The course first extensively explores the four major characteristics of aging: mortality, changing body composition, physiological deterioration, and age-related disease. To execute this broad spectrum aspect of the course requires faculty from the diverse disciplines of a health science university. The next phase of the course considers cellular and molecular alterations during aging and includes topics such as protein turnover, lysosomes, collagen, and immune responses. The third component of the course involves the anlaysis of the pros and cons of the major aging theories such as Programmed Aging, Error Hypotheses, Free Radical Theory, etc. Finally, experimental approaches for the study of aging are surveyed, e.g., the use of cells in culture and of food restriction in intact animals. This portion of the course also reviews the use of animal models for the study of aging including the unique requirements for the long-term maintenance of experimental animals.

Book Reviews

Monoclonal Antibodies to Neural Antigens, vol. 2. R. McKay, M.C. Raff, and L.F. Reichardt (Editors)
New York: Cold Spring Harbor, 1981, 282 pp., illus., index, $35

Monoclonal Antibodies to Neural Antigens consists of summaries of talks given at a meeting at Cold Spring Harbor in autumn of 1980. The stated purpose of this book is to "make this field (application of hybridoma technology) generally accessible and to help define the questions in neurobiology that may be answered using this new technique." Both objectives are realized, although the latter somewhat better than the former.

Monoclonal Antibodies is well organized and thoughtfully edited. The introduction, consistent with the two objectives of the book, first reviews the immunology needed to understand the remainder of the book and then summarizes the myriad of possible applications of monoclonal antibodies to neurobiology. The 26 contributions that follow are grouped either by the way in which the monoclonal antibody is used ("Defining Neuronal Cell Types and Cell Lines" and "Defined Antigens") or the system under investigation ("The Synapse," "The Retina," and "The Neuromuscular Junction"). Each individual contribution is short and succinct and usually begins with a clear statement of the problem and how monoclonal antibodies may contribute to its solution. The structural consistency between chapters, which greatly improves readability, is probably the result of careful editing.

Given the objectives of the book, its only limitation arises because the use of monoclonal antibodies in neurobiology is so recent. Consequently, although the goal of each contributor is to use monoclonal antibodies in order to learn something about the function of the nervous system, most of each chapter describes the generation and screening of antibody and characterization of antigen, with only preliminary results from experiments designed to evaluate the functions of antigens. The lack of more complete results from these experiments makes it difficult for the reader to understand exactly how monoclonal antibodies can be applied.

In summary, *Monoclonal Antibodies to Neural Antigens* fills an important gap in the literature. Previously there have been books on monoclonal antibody technique and a great deal on immunological methods in neuroscience, but this is the first to focus on monoclonal techniques in neuroscience. More importantly, it attempts, most often with success, to describe how the technique can be *applied* to the nervous system in order to understand *function.*

Corey Cleland
Northwestern University Medical School

The Pulmonary Circulation in Health and Disease.
G. Cumming and G. Bonsignore (Editors)
New York: Plenum, 1980, 405 pp., $47.50

This book contains the proceedings of a symposium held in Italy in July 1979. All of the participants were from European centers. The structure of the book is that of a manuscript followed by the discussion among the participants of the presentation. The areas covered include morphology of the pulmonary and bronchial circulations, the physiological and pathophysiological pressure-flow relationships, gas exchange, biochemical function of the lung, and physiological studies of cardiopulmonary interactions associated with lung disease.

On the whole this volume is relatively easy reading, with marked variability in the quality of the chapters ranging from superb to poor, as is invariably the case in any multiauthored book. The consistent strength of the book rests in the discussion following each chapter, despite the fact some of the discussion clearly refers to material presented at the conference but not in the manuscript. There are frequent, lively, and pertinent exchanges that illustrate the problems facing investigators in the field. It is in these that one enjoys a participant calling the speaker ever so politely to task for unwarranted conclusions. A number of chapters simply review a subject for background in a concise yet satisfactory manner, whereas others elegantly combine studies from their own laboratories with a literature review in a highly productive manner. The latter are particularly pertinent for readers in the United States, since some of the studies presented have been published in journals based in Europe, frequently in languages other than English. This was particularly evident in chapters by Gunella from Italy on the cardiorespiratory function in the syndrome of hypersomnia with periodic breathing, by Even et al. from France on the interaction between ventilation and circulation and bronchial asthma and pulmonary emphysema, and by Lee from England on the role of the pulmonary venous system and regulation of lung capillary blood flow and tissue fluid exchange. Indeed the chapter by Even et al. is one of the most lucid discussions of the subject that I have ever read. A number of the other authors have offered innovative and intriguing viewpoints in considering multiple aspects of the pulmonary circulation.

The typeset is large and easy to read. Except for the chapters on gas exchange involving multiple mathematical proofs, there is very little hard work required of the reader.

In summary this volume, though highly variable in quality, is a useful view of the work in pulmonary circulation going on the European continent, in particular presenting some useful information and references that would not usually be found crossing your desk. The organization of the chapter topics is, with a few exceptions, grouped in a reasonable fashion. I would recommend the text for purchase by departmental or school libraries.

I would like to end this review with two brief quotes from the discussion sections that are pertinent and reflect the character of this volume.

Dr. Grant de J. Lee, "There is a very fashionable tendency in my country and, I suspect in others, for undertaking something called 'medical research' that is doing the same experiment again, when in fact if you look at the literature there is a lot of varied information."

Dr. D. Heath, "I'm getting the distinct feeling, chairman, that Denolin doesn't understand my crude methods." Dr. G. Cummings, "I suggest that you sit down over a glass of vino rosso and sort it out. I hope that you have found the discussion enjoyable and perhaps even informative."

James L. Robotham
The University of Texas Health
Science Center at San Antonio

Hypothalamic Hormones.
J. R. Sowers (Editor)

New York: Academic, 1980. 342 pp., illus., index, $40

This volume is the fourteenth of a series in which papers key to the development of a given physiological topic are reproduced either in their entirety or in an edited form. Each group of papers is preceded by comments from the editor to set them in context. The idea of the series is a nice one, but for those with good library facilities such books may be regarded as a luxury. They may also remove the enjoyment that some find in turning up the original paper in its original journal. The fact that a Nobel prize was fairly recently awarded for work on this subject and the fact that we are witnessing the start of an even greater surge of interest in the topic makes it an opportune moment to produce a volume on hypothalamic hormones.

The task of selecting papers from the extensive literature is not an easy one, but the major landmarks have been covered. The editor has concentrated on the early studies that laid the foundation for our understanding of the nervous control of the endocrine system. Control of release has been covered from the stimulation studies of Harris through the pathways involved to the putative transmitters. The story is brought up-to-date with details of catecholamine neurons and opiate agonists in the brain. However, the CRF saga is not taken very far.

The selection of papers shows how the development of neuroendocrinology has depended on the efforts of relatively few workers, notably Geoffrey Harris. He investigated most of the pituitary hormones except for growth hormone and prolactin, which were not amenable to his methods of investigation. It is a pity that the sections dealing with Harris's technique of remote-control stimulation have been omitted from the facsimiles. His work depended to a great extent on the use of this technique. These experiments also illustrated what can be achieved with the imaginative use of equipment, much of it in this case home-built.

With the rapid expansion of the subject another volume will soon be required. It is interesting to speculate which of this year's crop of publications will be included.

Mary L. Forsling
Middlesex Hospital Medical School, London

Principles and Practice of Human Physiology.
O. G. Edholm and J. S. Weiner (Editors)

New York: Academic, 1981, 672 pp., illus., index, $88.50

This book grew out of the preparations for an M.Sc. course on applied human physiology and indeed provides an excellent textbook for such a course. Chapters have been prepared by lecturers on the course, all of whom are experts in the field. The title *Principles and Practice of Human Physiology* perhaps does not indicate the emphasis of the text, and possibly a title considered by the editors "The Physiology of Human Endeavour" would have done so better. This is in essence a reference book, and though principally aimed at the applied physiologist, it is of use to teachers of physiology in general inasmuch as it presents an integrated approach to the subject. It is especially valuable as a source of material for teaching medical students because they need to see the application of basic physiological principles. This can readily be achieved by considering the response to environmental stresses.

Interestingly the book opens with a cry against the universal use of S.I. units. While they are certainly of use in biochemistry, removing the confusion arising from the numerous ways in which concentration can be expressed, they produce some very cumbersome units in physiology, e.g., in the consideration of pressure. The information presented in later chapters is set in context by a brief but helpful chapter on the history of the subject. The study of human physiological reactions to a changing environment has developed rapidly with the advances in the appropriate technology. A chapter is indeed included on instrumentation. Much of the information included in this chapter, such as the details of the measurement of blood pressure, pH, and P_{CO_2}, is not specific to human studies. A description of temperature telemetry is included, but more details of telemetry in general would have been helpful as would further details on "Medilog." More information on measurement in humans and its value is given in a valuable chapter on the control of physiological parameters in critical illness. In studies on human subjects there is always the problem of the ethics of the investigation, and a useful concluding chapter deals with this aspect.

In addition to the more commonly considered environmental stresses, such as temperature and hypoxia, those encountered on exposure to topical situations, such as space travel, deep-sea diving, and flying high-speed aircraft, are considered. There could have been an overlap of information in the chapters on work physiology and locomotor and postural physiology, but they are complementary. Inevitably, because of the techniques available for measurement and the mass of background information, chapters concentrate on cardiovascular and respiratory responses, but other aspects are also considered.

In the examination of a new book, the acid test is the way in which one's own particular interest is handled. Unfortunately the neurohypophysis does not fare well. One would not expect oxytocin to be included, but vasopressin does seem to play an important part in fluid balance in a number of situations. None of the recent

results on vasopressin changes obtained with the use of radioimmunoassay have been included. There is even an error in the indexing. Under "vasopressin" we are told "see ADH." In fact the listing appears under "antidiuretic hormone." These points notwithstanding, the book is interesting and informative and would represent a valuable addition to any library.

Mary L. Forsling
Middlesex Hospital Medical School, London

Principles of Metabolic Control in Mammalian Species. R. H. Herman, R. M. Cohn, and P. D. McNamara (Editors)

New York: Plenum, 1980. 669 pp., ilus., index, $35

The title of this book is an appropriate description of its content. It is not written in classical textbook fashion, but rather it is an in-depth treatment of the major controls that regulate metabolism in mammalian systems. The book is arranged in 15 chapters with each chapter dealing with a major concept and bringing together many facets of information that are essential to that concept.

Chapter 1 dealing with general principles of metabolic control and chapter 2 covering nonequilibrium thermodynamics and noncovalent forces serve as an excellent introduction to the book. These chapters are presented in such a manner that the student of biochemistry and related basic biological science areas can read them with comprehension. Chapters 3, 4, 5, and 6 present the mechanism, modulation, and degradtion of enzymes as well as the regulation of protein biosynthesis. These chapters are well done and highlight the major enzymatic controls of metabolism without causing the reader to become frustrated with extensive minutiae. The regulation of protein biosynthesis is concise and clearly presented but is sufficiently inclusive to give the reader an understanding of the major mechanisms involved in protein synthesis.

Chapter 8, which deals with servomechanisms and oscillatory phenomena, was of particular interest to this reader. This is a topic that is frequently omitted or covered superficially in books of this nature. Again, the major concept is covered concisely with primary examples of feedback control. Chapter 11 is a very good presentation of membrane structure and transport systems. This chapter prepares the reader for chapter 12, "Cellular Mechanisms of Secretion." This is again an important concept that is too frequently omitted or poorly presented in many books but is well presented in this book.

The book is concluded with a discussion of the mechanism of action of hormones, chapter 14, and the biochemical basis of disease, chapter 15. This is certainly one of the best presentations that I have read on the subject of hormone action. Important factors of hormone action other than, but as well as, cyclic AMP are discussed.

To summarize, this book is well written and deals with the primary controls of metabolism. The topics covered are of major significance. The points made are well referenced, but the book is not encyclopedic. The figures and tables are clearly presented and intelligently selected. I find the book to be useful.

Chester E. Hendrich
Medical College of Georgia

Experimental Surgery in Farm Animals. R. W. Dougherty

Ames, IA: Iowa State Univ. Press, 1981. 146 pp., illus., index, $18.50

Experimental Surgery in Farm Animals is a useful book that helps fill the void in printed information on surgical procedures for research in cattle, sheep, pigs, and horses. The author has assumed a fundamental knowledge of surgical techniques, anatomy and physiology, and the book may therefore be more useful to the experienced surgeon than for the inexperienced surgeon. However, the novice surgeon may find the book of some value as general surgical procedures are referenced adequately, although references more current than those cited by the author are available in some cases. The reader may find the occasional anecdotes amusing or an annoyance.

Discussions of surgical procedures on the gastrointestinal tract (placement of rumen fistulas, cannulation of bile and pancreatic ducts, and chronic cannulation of portal vessels) were especially informative. The discussion of general procedures for cannulation of arteries and veins was disappointing. There was no mention of the use of Silastic blankets, which are glued to the catheter and used to anchor the catheter to the vessel wall. There also was no discussion of procedures for cannulation of fetal vessels or arteries and veins that supply the reproductive tract.

The use of a face mask for administration of halothane is recommended for induction of anesthesia. This assumes that the proper face mask is available. Second, the use of a tranquilizer is often required before the mask can be placed over the animal's nose. Heavy presurgical sedation may have several undesirable consequences, and for this reason many people prefer the use of a short-acting barbiturate for induction of anesthesia. The author does emphasize the necessity for intubation of the trachea in ruminants and the use of an inflatable cuff on the endotracheal tube to prevent aspiration of rumen fluid. Large endotracheal tubes with inflatable cuffs are difficult to obtain, and the discussion of the "homemade" endotracheal tube would have been of value if suppliers of the cuffs were listed. In addition, information on sources of large-animal endotracheal tubes would be very helpful.

The author devoted a great deal of attention to the design of an elaborate operating table. A description of possible alternatives, such as the inexpensive self-contained tilting tables or the use of padded mats on the floor, could be very informative for persons with limited budgets and/or less than optimal physical facilities.

These reviewers feel that the book would be useful for experimentalists interested in various surgical preparations for research studies.

W. C. Wagner and James E. Hixon
University of Illinois, Urbana