THE PHYSIOLOGIST

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Cover: Alan Chadburn Burton, 29th APS President, p. 66.

Alan Chadburn Burton
Biophysicist Extraordinary

All who knew him well would probably agree that Dr. **Alan Burton** (1904-1979) was one of the most colorful physiologists/biophysicists of the twentieth century.

His impressive height, red hair, and enormously bushy eyebrows arrested attention immediately. The slight stoop of the tall shoulders, the blue beret, and the booming voice were diagnostic, even at a distance, of Alan Burton walking the street in conversation with a friend. On closer acquaintance it was his utter enthusiasm, natural curiosity, and ability to ask deceptively simple scientific questions that made a deep and lasting impression. Alan had an uncanny knack of staying with a single train of thought. He would work out an idea on paper towels or the backs of envelopes, using his prodigious mathematical logic, and persist successfully in this activity in spite of, and even during, interruptions. It would often appear to the visitor that Alan had paid not the slightest attention to what was said, whereas in fact he had made a mental note of it for consideration later when his mind was free. Invariably, he would turn up trumps with the answer in a few days! When deep in thought he could continue a conversation unilaterally, oblivious of what the other party was saying. Yet he was far from unapproachable, always ready to listen to students' questions and to concern himself with their personal needs. Symbolic of this attitude his office door was always kept wide open, unless someone had come to discuss a matter confidentially; he could work oblivious of extraneous noise. We respected him first for the man he was and then as an outstanding scientist.

He was one of five children born in the elegant London (UK) suburb of Dulwich to Annie and Frank Burton. His father's dental surgery was located in one of the rooms of their home, and Alan always attributed his own unusual powers of concentration to the early discipline of doing school homework in an environment of noise—the shouts of his brothers and sisters and the screams of his father's patients! At Berkhampstead and the Strand School his education centered largely on classical studies, and there he developed the love of poetry that was to become a lifelong interest. At University College, London, he studied Mathematics and Physics, graduating Bachelor of Science (First Class Honors) in 1925. Those were the days of the Depression when jobs were scarce. He was fortunate to be offered a temporary post for 1925-26 as Demonstrator in Physics at University College and thereafter to obtain a position as a Science Teacher at Liverpool Collegial Institute. He enjoyed teaching, not merely because he enjoyed physics but also because he enjoyed people. During his years at University he spent part of each summer doing voluntary work, at a camp for boys from the slums of the "East End" of London. These boys all spoke a strong Cockney dialect; their "rhyming slang" both amused and intrigued him and extended his own vocabulary considerably! By contrast, at Liverpool his students' dialect was "broad Lancashire." From these first-hand encounters there developed the gift of mimicry with which he was later to enliven many a meal-time conversation.

While sitting on a park bench in Liverpool and reading *The Times* newspaper, he came across an advertisement from the University of Toronto for a "Physical Assistant" to set up experiments for the undergraduate physics lectures by the Department Chairman, Prof. J. C. McLennan. He applied for the job, was the successful candidate, and at the age of twenty-three came to Canada. McLennan, recognizing a good thing when he saw it, invited him to work for a graduate degree, and the following year (1928) Alan successfully defended his M.A. Thesis, entitled "The absorption spectra of the major planets." Following this he began doctoral research in Physics, at Toronto, and received the Ph.D. in 1932 for a thesis on "Heating of electrolytes by high frequency currents."

This time marked Alan Burton's entry into the world of biology and the start of his career as a biophysicist, for one of the six papers arising from his doctoral research was entitled "Selective heating by short radio waves, and its application to electro-therapy" (*Can. J. Res.* 4, 1931). The topic was then of great medical interest, since artificial fever by electromagnetic heating was in vogue. He found himself explaining to physicians and students the heating of body tissues by short-wave radiation and developed an interest in the measurement of skin temperature and heat exchange. This led him

Alan Burton's imprint on the American Physiological Society goes far beyond the fact that he was the second Canadian to hold the office of President. He served two years as a member of the Council before becoming President-Elect. During this time he traveled to 10 different centers throughout the United States to discuss with audiences the problems that would be encountered by the Society once its membership reached 3,000. Two solutions reached by Alan Burton wer to hold several meetings of the Society each year, similar to the concept of the Society's fall meetings, and to create a publication, now *The Physiologist,* for the membership. He also was responsible for the creating of the Associate Membership category during his term as President and for the development of the Society's role in the area of international physiology.

Note: An "In Memoriam" following Alan Burton's death was included in the *Physiologist* [23(1): 17-18, 1980].

(1932-34) to join Prof. J. R. Murlin of the Department of Vital Economics, University of Rochester, NY, to do research on human calorimetry. He was awarded (1934-36) a Training Fellowship in Biophysics from the General Education Board of the Rockefeller Institute, which was tenable at the Medical School of the University of Pennsylvania. Here he worked with Prof. H. C. Bazett on human temperature regulation and peripheral blood flow. He always remembered with great affection that it was Bazett who showed him that Physiology is fun! The next four years were spent as a Research Fellow with Dr. Detlev Bronk at the Johnson Foundation for Medical Physics, University of Pennsylvania. There Alan wrote what he later considered to be his best scientific paper, "The properties of the steady state, compared to those of equilibrium as shown in characteristic biological behaviour" (*J. Cell. Comp. Physiol.* 14: 327-349, 1939). This paper is a superb example of clear thinking and is well worth the reading. It was at this time also that his first invited review article "Temperature regulation" was published (*Annu. Rev. Physiol.* 1: 109-130, 1939).

After the outbreak of World War II, Alan returned to Canada to undertake work of national importance. He was assigned by the National Research Council to aviation medical research, and the development and testing of protective clothing and equipment for all services, at the Banting Institute, University of Toronto. During the period 1940-45 he submitted to the NRC numerous reports on ad hoc problems, 51 on aviation medicine and 12 on protective clothing; needless to say, these reports were "classified." In the open literature there appeared only three papers based on work carried out at this time, the first of which was the result of a bright idea while Pharo Gagge, Alan Burton, and H. C. Bazett were swimming together in the University of Toronto pool. These men were all fighting the cause of Thermal Physiology in Toronto and working with G. Edward Hall's Committee on Flying Clothing. As they splashed about in the water they complained loudly that engineers always spoke in terms of BTU's, feet, and pounds, whereas physiologists spoke in terms of calories, centimeters, and grams, and neither group understood or trusted the other. In the clothing business, the two prime units of interest were clothing insulation and metabolic energy; that is how they thought up the *Clo* and *Met* units, which were named by Bazett with a great guffaw! The result was the paper "A practical system of units for the description of the heat exchange of man with his environment" by A. P. Gagge, A. C. Burton, and H. C. Bazett (*Science* 94: 428-430, 1941).

Alan Burton spent the summer of 1945 in Germany as a member of the Enemy Science Technical Intelligence Team. Photographs of him at that time, taken in Frankfurt by Dr. Bruce Dill, appeared in the October 1984 issue of the *Physiologist*. At a National Research Council press conference in Ottawa, December 1945, twenty-five Canadian members of the Intelligence Team gave as their unanimous opinion that German science as a whole was behind the rest of the world. The underlying reason for this was provided by Alan Burton, who declared, "Science cannot flourish without freedom. It cannot work in a totalitarian State."

When G. Edward Hall became Dean of Medicine at the University of Western Ontario in 1945 he invited both Alan Burton and Pharo Gagge to go there as Biophysicists. Since Gagge had taken a regular commission in the new US Air Force as a Scientist in Uniform, he was unavailable. Alan was appointed Assistant Professor of Medical Research in 1945 and two years later the University took the enterprising step of creating the first Department of Biophysics in a Canadian medical school, Alan being given the position of Associate Professor and Chairman. He was promoted to Full Professor in 1948. In the years that followed he received numerous invitations to accept prestigious positions in the United States; these he invariably turned down. His feelings were (in his own words), "I'm a Canadian. I love my American friends but I love my Country, and I want to stay here." At Western he worked unhampered to develop the new discipline of Biophysics, gathering round him a superb group of graduate students, many of whom have gone on to establish international reputations in research and occupy distinguished positions in Canada and the United States.

From the biophysics of heat exchange with the environment his interests moved on to the biophysics of the peripheral circulation. However, he set in order his thoughts about heat exchange in the book *Man in a cold environment*, published together with Otto Edholm (who spent a short period at Western as Chairman of the Physiology Department) in 1955. This book was reprinted unchanged, fourteen years later, and is still regarded as a classic. Many papers on the biophysics of blood vessels and blood flow came from Alan Burton and his students, and in 1962 these were followed by the well-known chapters "Physical principles of circulatory phenomena, the physical equilibrium of heart and blood vessels" (*Handbook of Physiology: Circulation* 1) and "Properties of smooth muscle and regulation of the circulation" (*Physiol. Rev.* 42). From his experience teaching cardiovascular physiology to medical students there came his second book *Physiology and Biophysics of the Circulation*) (1965). In the preface he wrote:

> By concentrating on ideas more than on facts, the author hopes to give more permanence to any value this monograph may have, for new "facts" of physiology are added and old "facts" amended so fast, by modern physiological research, that a purely factual monograph is out of date before it reaches print.

This book, translated into French, German, Italian, Japanese, and Spanish, has been widely appreciated by medical students, as evidenced by the hundreds of letters he received from them. After his retirement he prepared a second edition, published in 1972.

His interests moved from peripheral circulation to the geometry and mechanics of erythrocytes, the deformability of membranes and permeability, and finally to intercellular communication and the theories and epidemiology of cancer. He demonstrated (*Eur. J. Cancer* 11: 365–371, 1975) a marked reduction of cancer rates at altitude and suggested that the mechanism is related to the persistent decrease in base excess (buffering power) of the blood. It is tragic that his third book *Understanding Human Cancer: the Physiological and Biophysical Point of View*, completed just before his death and subsequently reaching galley proof stage, may never see the light of day because of the bankruptcy of the publisher. He personally trained 14 M.Sc. and 22 Ph.D. students and started at Western in 1966 Canada's first undergraduate program in Honors Biophysics, which still bears much of the imprint of its founder. He is the only person to have been elected President of the American Physiological Society (1956), the Canadian Physiological Society (1959), and the Biophysical Society (1966). He served as Chairman of FASEB (1957-58) and its Canadian counterpart, CFBS (1963), and received a Gairdner Foundation Award (1961).

Alan Burton has probably been appreciated most for his ability to make understandable to nonphysicists the application of physical laws to biology. He believed, and exemplified in person, that the arousal of interest is paramount to success in teaching. He made the study of the physics of living things relevant, exciting and, above all, fun. Sure, he was an absent-minded Professor, who on several occasions set his jacket on fire by placing his lighted pipe in his pocket and whose driving of an automobile was, to say the least, remarkable! But these shortcomings had to be weighed against the surprising insight shown in the questions he asked following seminars. His was a vigorous and penetrating mind, with a startling ability to see through to the nucleus of the problem and pose the essential question that provided others with a fresh direction for their research.

He was a superb raconteur. All his stories painted indelible impressions of people or things, and many of them contained hidden bits of scientific knowledge. He loved humor, and at a conference on "Cold" held in Alaska it was his idea that Robert Service's poem "The Cremation of Sam McGhee" should be read at the start of the meeting and be published in the proceedings. He was very proud that his suggestion was implemented! He would often use humor to convey a serious point more readily, and this was reflected in the titles of some of the talks he gave: "Biophysics, humble pie for inflated physicists" (*Phys. Can.* 8: 6–46, 1953); "The stirring of the biophysicists" (President's message: APS Newsletter, Nov. 1956); "Fashions in American physiology" (*Physiologist* 6: 319–323, 1963); and "A virtue of ignorance. A biophysicist asks simple questions about medicine and medical research" (*Ann. R. Soc. Physicians Surg. Can.* 1: 192–201, 1968).

Alan believed wholeheartedly that the true motivation of the scientist is curiosity, not the hope of utilitarian rewards (his example: "Better things for better living through chemistry"). He admired greatly Michael Faraday's (1791-1867) handling of the question asked by a lady at the end of a public lecture, "What use is all this?" Faraday replied, "What is the use of a new-born baby?" Alan immortalized this incident for his students in doggerel verse, as follows, and made the point stick.

Apology for Science

Mr. Michael Faraday, of the Royal Institution,
Gave public lectures every month, complete with demonstrations,
With rods of ebonite and sealing wax
And fur of cats, and Leyden jars
And magnets swinging on a thread
And piles of copper plates, and pumps and flasks
And all festooned with mathematics.

Earnest students, and the patron rich,
Idle ladies, and the sheltering bum,
And even now and then a Royalty
Would fill the floor and galleries,
Gossiped, yawned, took tidy notes
Or slept.

A smug old lady of the lecture-loving kind,
Joined the admiring after-questioners and said:
"Mr. Faraday, all this is very fine, most interesting
and Oh, so very clever.
But will you tell me please,
What use it is?"

The scientist replied:
"Madam, will you tell me –
What is the use of a new-born child?"

And ever since, when people hear
Of studies on metabolism of the ant,
Of chromosomes, contractile vacuoles, chlorophyll,
The sex-life of the beetle, resonance in molecules,
Or photo-synthesis,
They tell this tale, and usually explain
That babies grow to Presidents, or Henry Fords, or Edisons,
Or anyway to carry mail, or dig, or sweep –
And who can tell?

Of course it's difficult to see how this applies
to History and Classics,
Research in Anthropology or Cosmic Evolution
And other really useless studies.
But here we recognize
That the really cultured social hide supports,
Like fleas upon contented dogs,
Permitted parasites.
What a travesty in this, on Faraday and Science!
Are babies born, conceived for usefulness,
Planned as prospective workers, raised like stock?
Or is it Love, or innate Constitution?
Must not the sons of men, because they are,
Create and procreate?
And madam . . . have you never met
The proud new parent, driven by the urge to tell
Each precious infant detail?

Ah, no . . . it is the nature of the beast
That maggots breed, that dogs must bark
And scientists investigate.
The faith of Faraday endures . . .
There is a Pattern, by whatever Loom,
And men by search must find it.

(From *Phys. Can.* 8, 1953)

Association with Alan Burton over the years leaves an accumulation of memories of a rare man, a man whose perception commanded international respect and yet whose humility made him accessible to every level of student. Graduate students and faculty alike realize that the best course they ever took had no number, no slides, no handouts, no examinations – just Dr. Burton at tea.

Alan C. Groom, Chairman
Department of Biophysics,
University of Western Ontario.

John McArdle. . .

Discusses The HSUS and Its Efforts to Repeal Pound Release Laws and Its Goals for Laboratory Animal Use

The Human Society of the United States (HSUS) has announced that one of its priorities for the remainder of the 1980s is to abolish the practice of releasing unclaimed pound animals for use in research and education.

To accomplish this goal the HSUS has initiated two thrusts: *1*) seeking federal legislation that would prohibit the use of government funds for any research involving pound animals; and *2*) conducting and supporting a nationwide campaign encouraging state and local governments to enact laws barring the release of unclaimed pound animals to research and educational institutions.

Currently there are nine states with laws prohibiting the release of any unclaimed animal except for the purpose of pet adoption. Similar legislative proposals are expected to be considered this year in at least 30 states.

The HSUS believes that the combination of additional state and local laws prohibiting the release of unclaimed animals and Congressional restrictions on research appropriations will be sufficient to effectively halt the use of pound animals and that this goal can be achieved by 1990.

Dr. John McArdle, who is the HSUS's director of laboratory animal welfare, will direct the society's efforts toward accomplishing this goal. Dr. McArdle has been with the HSUS since 1983. Prior to that time he was an assistant professor in biology or anthropology departments at universities in Illinois.

Dr. McArdle's academic credentials include a doctorate in anatomical sciences from the Department of Anatomy of the University of Chicago. His area of specialization was the biomechanics and functional anatomy of the locomotor system in primates. Dr. McArdle currently maintains an active research program in Egypt, working as a consultant on zooarchaeology and paleoecology to major archaeological expeditions.

To learn more about The HSUS's goals and its other interests in the use of laboratory animals, the American Physiological Society asked Dr. McArdle these questions:

Until recently the question of releasing unclaimed pound animals to research and educational institutions was an issue promoted largely by animal right groups. What motivated the HSUS to take the lead role in this issue at this time?

It is inappropriate to make a clear-cut distinction between animal rights and animal welfare organizations, as well to attempt to subdivide their respective areas of activity. What exists today is an animal welfare/rights movement, with a common set of concerns and goals. Although the groups may differ with respect to strategy, tactics, or areas of concentration and expertise, they all share the same basic philosophical foundations.

Historically, pound seizure has been opposed by animal welfare (not rights) organizations. The issue has been a major concern of the HSUS since it was founded in 1954. In fact, a major factor in the formation of the HSUS was the need to actively fight the increasing incidence of pro-pound seizure legislation that characterized the early 1950s.

Throughout its existence, the HSUS has opposed pound seizure and played a key role in local and state efforts to prohibit the practice. The expanded emphasis in recent years is due to heightened public and political awareness of the problem, and the abundance of new information to support our position on the increasing thefts of pets for sale to research facilities and a growing realization that pound seizure, as an issue, encompasses all the traditional areas of concern for animal welfare/rights organizations. The growing trend towards pro-animal activism and direct public involvement in the process of promoting welfare/rights issues provides a solid base of support for our programs.

By taking the lead role, does this indicate in any way that the HSUS has philosophically shifted more closely to the philosophy of the animal rights movement?

The HSUS considers itself to be an animal rights organization in that it supports the philosophical position that animals are not commodities; are not tools to achieve human ends; have an existence, wants, and needs independent of humans; and have certain inalienable rights that must be respected and protected. It is not permissible or desirable to allow a violation of those rights simply to provide a "benefit" or "convenience" for humans.

Assuming a leadership role in the efforts to end pound seizure is a logical extension of our concern for the rights of those animals.

The new formed National Coalition to Protect Our Pets, composed of animal rights and animal welfare groups including the HSUS, is reported to have been organized to work toward the elimination of pound release laws at the state and local levels. What will be the HSUS's role in this coalition?

The HSUS was instrumental in the initial formation of the National Coalition to Protect Our Pets (Pro Pets). Three HSUS staff serve on the committees directing the activities of the Pro Pets, with John A. Hoyt, President of the HSUS, serving as Chairman of the management committee. As with the other members of this historic coalition, the HSUS will provide logistic, financial, staff, or any other assistance that Pro Pets may require in order to more rapidly achieve its goals. We anticipate our role will vary, depending on the specific situation. Further, as appropriate, the HSUS will continue its own antipound seizure efforts.

Is the eventual goal of the HSUS to abolish the use of all animal models for purposes of research, education, experimentation, and testing?

The Humane Society of the United States recognizes that benefit for both animals and mankind has been achieved through some scientific research and testing on animals but that the advancement of medicine and human health has also been hindered by an overemphasis on such animal research. It recognizes that uses of animals in biomedical research, safety testing, and other programs are many and varied and that this research and testing is not likely to end in the immediate future.

The HSUS believes that millions of laboratory animals do suffer severely and needlessly in painful experiments, resulting from exposure to noxious substances and pathogenic organisms, or from cruelty, carelessness, ignorance, and indifference. The HSUS also contends that toxicity testing on live animals, as now required by government agencies to test the safety of serums, drugs, cosmetics, and other chemicals, is often unreliable, inaccurate, and unnecessary and should be replaced by new methods not involving animal suffering.

The HSUS also expects that scientists and facilities using experimental animals should be held strictly accountable for their care and use and should keep animals in a manner fulfilling both physical and behavioral needs. Experiments should be rigorously planned, with proper statistical design, so as to minimize the number of animals necessary to be used to achieve reliable results and, through the administration of anesthesia and analgesics and other appropriate medication and veterinary care required, to preclude animal suffering.

Therefore, the HSUS strongly advocates the development and application of alternative methods of research and testing, which could reduce the number of animals required, refine existing techniques and procedures so as to minimize the level of stress endured by an animal, and replace the use of laboratory animals. Refinement and reduction are interim steps toward the ultimate long-term goal of complete replacement of animals in biomedical research, product testing, and education.

How many members does the HSUS have on its rolls and what percentage of this membership is known to be opposed to the use of unclaimed pound animals for the purposes of research and education?

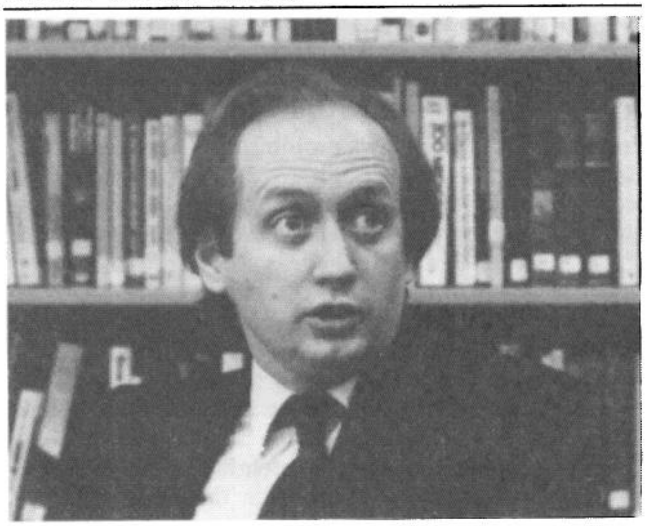
The HSUS is growing rapidly and presently has a constituency of approximately 500,000 individuals. Although we have not polled our entire membership on this issue, I have only received one letter from a member critical of the HSUS position on pound seizure. In that particular case, the problem resulted from false statements made by a physician regarding the necessity of using pound dogs in research related to their son's illness. If there are individuals in the HSUS who support pound seizure, I am convinced they represent an insignificant percentage of the entire membership.

What control, if any, does the HSUS have over local humane societies as to policies of releasing unclaimed pound animals?

The HSUS does not operate animal shelters. It does, however, have extensive programs involving both public and private shelters, and is highly respected by the organizations and agencies managing these facilities. While most of these shelters decline to release animals for research, testing, or teaching purpose by reason of their own policy or initiative, many look to the HSUS for both guidance and support on this issue. Nearly all the cats and dogs released for use in biomedical research and teaching come from municipal and county facilities. The small handful of humane societies that provide animals for such purposes are atypical and probably do not fully understand the negative implications of their actions.

Whether shelters are public or private, the HSUS believes there is a direct correlation between the success of their various programs and their position on pound seizure. The proper function of a shelter is to act as a last humane refuge for animals who have lost their owners and not as warehouses to supply "cheap," subsidized animals for use in laboratories.

Despite assertions to the contrary by the research community, all of these animals (unless second or third generation feral individuals) are pets. We define a pet from the perspective of the cat or dog and its socialization history with and expectations of humans. It is irrelevant to that definition whether or not the owner remains with the animal.



The HSUS works with humane societies and local governments to promote proper operation of their shelters, to provide humane sanctuary for the animals and either redemption, adoption to a suitable home, or humane euthanasia by caring individuals. The HSUS has a rigorous accreditation program (the functional equivalent to the role of AAALAC in the research community), to which shelters can apply. The first requirement of accreditation is that no animals be released for research, testing, or education.

Finally, the HSUS has now clearly established that the public perception of the shelter has a direct impact on animal control activities and other programs. In a 1982 survey of 2,200 shelters and animal control agencies, 93% of those responding stated that the release of animals for research undermines effective animal control programs and individual pet owner's confidence in their local shelters.

We are the experts in this field, not the research community. The existence of pound seizure interferes with everything humane societies represent and attempt to accomplish in their local communities.

Nine states have enacted laws restricting the release of pound animals. Which one of these state laws would the HSUS like to see duplicated in states considering such legislation and why?

If this were "the best of all possible worlds," the HSUS would prefer to duplicate, as closely as possible, the legislation passed in Massachusetts in 1983. There are several important aspects to that law in addition to the prohibition on pound seizure. In all antipound seizure campaigns, we strongly encourage the inclusion of a provision banning the importation of pound animals into a state. Unless such interstate shipment is ended, the threat to pets from pound release, fraud, and theft will only shift geographic locations, rather than stop. We intend to entirely cut off the supply of pet-type animals from all sources

In addition, the Massachusetts law identifies humanely acceptable methods of euthanasia, permits unannounced inspections of research facilities by humane officers, and requires licensing of such facilities. The HSUS believes these provisions are important. In particular, it is time for states to stop having two sets of cruelty laws, one for the general public and a weaker one for the research community. Cruelty does not cease to exist by simply moving the activity within the four walls of a laboratory.

You have been quoted as saying that a Congressional restriction on research appropriations and the enactment of additional state laws will be sufficient to effectively eliminate the practice of pound release. What do you believe to be the minimum number of states now needed to enact such laws?

Rather than identify a minimal number of key states, the HSUS and the Pro Pets Coalition intend to continue our efforts until pound seizure is prohibited in all 50 states and restrictions on the use of federal money for both intra- and extramural research have been put in place. We are currently moving towards achieving both of these goals.

Other than the restrictions the HSUS is seeking on research appropriations, what other laws would the HSUS like to see enacted by the Congress regarding the use of laboratory animals?

At present, the HSUS Congressional agenda focuses on six key areas. These are *1*) banning the use of animals for the training of Department of Defense students and personnel in the treatment of ballistic wounds, *2*) promoting specific allocations of funds for the development of new alternative techniques, *3*) changing the seven regional primate research centers into national centers for the development of alternatives, *4*) passage of the Dole and Brown Bills, to address the serious weaknesses that exist in the current Animal Welfare Act, *5*) passage of the Torricelli bill, HR 1145, and *6*) support for the Walgren provisions of the NIH Authorization Bill.

In recent years, both APS and the HSUS have presented Congressional testimony urging the Congress to increase its appropriations for the Animal and Plant Health Inspection Service (APHIS) so that it can provide a more viable service in the monitoring of animal facilities. Now, the Reagan Administration is proposing the elimination of APHIS. What is the HSUS's position on this proposal?

The HSUS is unequivocally opposed to the Administration proposal. This is an area where both the research and animal welfare/rights communities share a common interest. We also want APHIS to spend its budget on inspections and more rigorous enforcement, rather than deliberately allowing surpluses to accumulate or using such funds for purposes unrelated to the Animal Welfare Act.

Despite its many faults, APHIS needs to be significantly strengthened, not eliminated. Needed improvements include *1*) stiffer penalties and swifter enforcement, *2*) a general shift in emphasis from compliance to enforcement, and *3*) the adoption of provisions that give private citizens standing to sue APHIS for failing to perform its duties properly.

Should APHIS be eliminated by the Congress, will the HSUS seek an active role in taking responsibility for the inspection of animal facilities, as suggested by the Reagan Administration?

The HSUS has neither the financial resources nor sufficient personnel to attempt to replace the role currently assumed by APHIS. Although I have no doubt that

representatives of humane societies, given proper training, would be more motivated and productive than the average APHIS inspector, I seriously doubt research laboratories would welcome unannounced, comprehensive inspections by our people. This would be especially true if we had the power of enforcement.

The only viable long-term solution to the yearly APHIS funding crisis and the poor performance of APHIS personnel (i.e., inspectors, administrators, and legal counsel) is to make the system self-sustaining and to employ a sufficient number of properly trained animal welfare specialists.

What is the HSUS's position concerning the breakins and theft of laboratory animals by the Animal Liberation Front?

The HSUS neither condones nor condemns the action of the Animal Liberation Front (ALF). We do, however, understand the frustration such individuals feel with the failure of existing laws, regulations, guidelines and federal agencies to protect laboratory animals. These perceptions are further enhanced by the arrogance and intransigence of the biomedical research community, with its refusal to admit that serious problems exist with both the care and use of animals in research, testing, and teaching laboratories.

We suspect that the concerns of the research community result not from any serious threat to biomedical research, but rather from the fact that in each instance where the ALF has entered a laboratory they have found and documented multiple, existing difficiencies in the care and use of the experimental animals.

As long as biomedical research remains basically a closed system, unaccountable directly to the general public and fails to seriously address the legitimate concerns of that public, it will have no one but itself to blame for the continued existence of and apparent widespread public sympathy for the ALF.

APS has proposed a Congressional amendment to the Animal Welfare Act that would make such breakins and thefts a federal offense. Would the HSUS support such an amendment to stem this malicious mischeif?

The HSUS Board of Directors has not taken a position on the proposed amendment. However, APS has not convincingly established that the actions of the Animal Liberation Front are, in fact, such a serious threat to biomedical research laboratories that a special amendment to the Animal Welfare Act is necessary. ALF actions simply do not occur that often. Further, since the ALF breakins already violate several existing federal laws, there is no justification for duplicative legislation.

A more serious concern for the HSUS is the possibility that the proposed amendment would be used to control and censor media access and use of documentation of abuses, cruelty and substandard care provided by the ALF. We suspect this is the principal motivation behind the APS amendment.

It is difficult to justify special federal legislation related to actions involving a few dozen animals, when documented instances of abuses involving thousands of laboratory animals have gone unpunished.

Who Would You Like To Know?

The purpose of this feature is to provide members of the Society with insights to a variety of issues and, hopefully, to give the answers to questions you would like to ask such individuals.

If you have someone in mind you would like to see featured in a future "People You Should Know" interview, please let us know.

William M. Samuels, APS

Aside from seeking an end to pound release practices, what other concerns does the HSUS have concerning laboratory animal welfare?

We divide our concerns into two broad categories: care and use. With respect to care of laboratory animals, we want *1*) the formulation and implementation of guidelines based on species specific environmental and behavioral requirements, *2*) an emphasis on optimal rather than minimal standards, *3*) inspections of laboratories by state humane officers, and *4*) required comprehensive training of all laboratory animal technicians, caretakers, principal investigators, and graduate students in proper methods of care and use of laboratory animals.

On the use side of the issue, we want *1*) to open the peer review system to public participation and accountability at all levels, *2*) a comprehensive classification of experimental techniques, with specific prohibitions of the most inhumane methods, *3*) elimination of the Draize and classical LD_{50} tests and a greater emphasis on developing and adopting alternative methods, *4*) a ban on the use of nonhuman animals in experimental psychology laboratory investigations, *5*) a ban on warfare related experiments and tests on nonhuman animals, and *6*) reduction and eventual elimination of research and testing of such uniquely human addictions as tobacco, alcohol, and drugs and such medically nonessential items as cosmetics. The vehicle the HSUS has identified to accomplish these goals is the development of alternative methods and techniques, rather than a continuation of established traditions.

In light of these concerns, do you have any words of wisdom that you would like to share with physiologists?

I do not expect my comments to be perceived as wisdom, but I have some very general concerns about the attitudes and positions taken by the research community with respect to our efforts to stop pound seizure. Although there are individuals opposed to pound seizure who also want all research stopped, this is fundamentally not an antiresearch activity. We have other programs to deal with problems relating to biomedical research. It is also abundantly clear that irrationality, emotionalism, lack of objectivity, and misrepresentation do exist within the research establishment.

If the research community views the current efforts to stop pound seizure as a gladitorial contest, you have made a grave error by drawing the line at the pound door.

President Wants to End Federal Enforcement of Animal Welfare Program

Now that the Congress and several federal agencies are giving serious attention to stricter enforcement of federal animal welfare regulations, the Reagan Administration is proposing to eliminate the government's principal enforcement agency.

In the Administration's budget proposal for Fiscal Year 1986 it is stated that the US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) would contain its activities to the monitoring of animal disease and pest control.

The President's budget message said: "APHIS will discontinue all inspections of licensed dealers, research facilities, exhibitors, and carriers. There will be no Federal investigations of complaints or alleged violations and cooperative efforts with other governmental agencies will cease.

"Given current fiscal constraints the Department (of Agriculture) must concentrate limited resources in areas which will protect American agriculture from pests and diseases. Consequently, the Department proposes to eliminate the animal welfare program."

The Administration also proposes that "states, industry, and humane groups should take responsibility for the humane treatment of animals."

This is the third consecutive year that the Administration has targeted APHIS, but until now such efforts have been aimed at reducing the funds for the animal welfare programs and not the elimination of all APHIS activities except for animal disease and pest control.

In previous years the Administration had suggested that APHIS work with states, industry, and humane groups in the enforcement of federal animal welfare programs. However, the elimination of APHIS as an enforcement agency could, in effect, negate the Animal Welfare Act until it is determined what enforcement powers, if any, the federal government can grant to non-federal entities for the enforcement of federal laws.

In light of recent events it seems doubtful that the Congress will go along with the President's proposal. First of all, the Congress' own independent fact-finding body—the Office of Technology Assessments—is expected to report in late summer on its two-year study of laboratory animal issues.

It is anticipated that the report will show that APHIS is a viable agency which, by and large, has been hindered in its efforts because of inadequate funding.

Also, the Congress has rebuffed the previous attempts to cut APHIS funding by continuing the appropriation of $4.7 million for the animal welfare programs. (The agency has stated that to be effective in its role as the enforcement agency for the Animal Welfare Act it needs approximately $7 million annually.)

The Congress also is aware that support for APHIS, including support for full funding at $7 million, is the one area that both the research community and the animal welfare organizations are in complete agreement. APS has had a lead role in representing the research community in support of APHIS funding.

Additionally, the Senate and the House have both expressed strong interests in maintaining the Animal Welfare Act. Both chambers introduced bills in the last session of the Congress to amend the Act and interest in this area is continuing in the current session of Congress.

Lastly, several federal agencies, including the departments of Defense and Health and Human Services, are actively engaged in revisions of criteria for their animal welfare programs.

Scientists Menaced by Animal Activists

Animal rights organizations in Great Britain, Canada, and the United States have stepped up their campaign against the use of laboratory animals. The most severe among these stepped up activities since the first of the year include the following.

Great Britain

The home of Sir John Vane was one of nine homes fire bombed this year by the Animal Liberation Front (ALF). It was the second fire bombing of Sir John's home. Sir John is a Nobel laureate and last April in St. Louis gave the APS' "Perspectives in Physiology" lecture.

The other homes bombed were colleagues of Sir John's at the Wellcome Foundation's research laboratories. The ALF also paint bombed some homes, smashed windows, and slashed tires. A warning was also issued by the militant animal rights group that other scientists can expect fire bombings of their homes.

Canada

The ALF broke into a research laboratory at the University of Western Ontario and stole three cats and a monkey. Following the break-in another animal rights group, Lifeforce, placed criminal charges of animal cruelty against two researchers.

Since that time, one of the researchers has been harrassed with threatening telephone calls and letters, his family has been followed openly whenever they go out, and a protest demonstration was staged in front of his home by 50 animal rights activitists. A neighbor, protesting the demonstration, had his clothes ripped from his back by the activists.

The break-in was the fourth in the last year at Canadian research universities.

United States

Letters and telephone calls threatening death have been received by five University of California-San Diego researchers. The ALF has claimed credit for issuing the threats.

One telephone threat told a professor that he would be shot in the head if he did not cancel his course. Another

scientist, whose home also was vandalized, received two death-threat letters, one which had a photograph of him with a gun sight focused on his face.

A Los Angeles animal rights activist, who is president of Students United Protesting Research on Sentient Subjects, said that San Diego has been targeted for intensified activity against animal research.

Nevada Kills Dog Bill; New Bill in Massachusetts

The Senate Natural Resources Committee of the Nevada General Assembly has killed a bill that would have restricted the use of live animals in research. The bill had been introduced at the request of the Humane Society of Southern Nevada, a frequent critic of research at the University of Nevada medical school.

The issue had been a year-long battle that included demonstrations at the University hospital and a bomb threat which closed the medical school. Nevada had been perceived as a "soft state" in which animal rights legislation might slip by unnoticed.

Following the committee's rejection of the bill 18 Nevada legislators introduced a pet protection bill that permits the release of animals by the pound as long as the animal's former owner does not object in writing to the release. The Humane Society is opposing the bill and the university is supporting it.

The bill also includes provisions for the prosecution of anyone breaking into a research facility and stealing or destroying laboratory animals, research data, and equipment as well as the prosecution of anyone who possesses any item stolen from a research laboratory. This provision of the bill is patterned after the APS proposed amendment to the Animal Welfare Act.

The Massachusetts General Assembly has been presented with a bill that would prohibit the continuation of research involving greyhounds.

The bill, entitled "An Act to Protect Dogs Used for Racing Purposes," states that dogs raised, trained, or used for racing or race track purposes, including all greyhounds, cannot be used for research, testing, experimentation, demonstration, or instruction purposes within the Commonwealth of Massachusetts.

Considerable research in behalf of the greyhound racing industry is being done in Massachusetts. In December 1983 the Massachusetts General Assembly enacted the strictest law in the nation regarding unclaimed pound animals. By October of 1986 no unclaimed pound animal from within or from outside of the state can be used for research.

Rep. Waxman Urges Funding for 6,500 Grants

Rep. Henry A. Waxman (D-CA) has introduced a Senate-House resolution urging the Congress to make funds available to the National Institutes of Health for 6,500 new and competing grants for individual investigator-initiated research in Fiscal Year 1985.

The US Office of Management and Budget ordered the funding of only 5,000 new grants, which is 1,500 less than what the Congress appropriated funds in passing Public Law 98-619.

William M. Samuels, CAE

Announcements

Conference on Autoimmunity – Experimental and Clinical Aspects

A Conference on Autoimmunity – Experimental and Clinical Aspects sponsored by the New York Academy of Sciences will be held at the Barbizon-Plaza Hotel, New York City, on 17–19 June 1985. This meeting will review the substantial progress made in the field during the past two decades. Invited speakers will cover the major topics of the conference including the interplay between self-recognition and lymphocyte circuits, idiotypic control, genetic regulation, effector mechanisms, immunoregulatory factors, and new animal models of autoimmune disease. A final session will deal with fresh approaches to the treatment of autoimmune diseases. *Information*: Conference Department, The New York Academy of Sciences, 2 East 63rd St., New York, NY 10021.

MIT Course in Design and Analysis of Scientific Experiments

The Massachusetts Institute of Technology will offer a one-week elementary course in Design and Analysis of Scientific Experiments, 15–20 July 1985. Applications will be made to the physical, chemical, biological, medical, engineering, and industrial sciences and to experimentation in psychology and economics. *Information*: Director of Summer Session, Room E19-356, Massachusetts Institute of Technology, Cambridge, MA 02139.

Symposium on Proteins of Excitable Membranes

The 39th Annual Symposium of the Society of General Physiologists, Proteins of Excitable Membranes, will be held at the Marine Biological Laboratory, Woods Hole, MA, on 4–7 September 1985. *Format*: Invited lectures on structure and function of ACh receptor, Na channel, Ca channel, and cation translocation ATPases, posters, and abstracts concerning ionic channels, transport ATPases, and related topics. *Deadline date for abstract*: 15 May 1985. Apply for limited housing by August 1, 1985. *Information*: Soc. Gen. Physiologists, PO Box 257, Woods Hole, MA 02543.

Genetic Engineering of Animals

A program on Genetic Engineering of Animals: An Agricultural Perspective will be held at the University of California, Davis, on 9–12 September 1985. It has been designed to appeal to a broad audience in animal research and increase awareness of how genetic engineering research may aid future research efforts and animal agriculture. Concepts, applications, and future applications will be featured. Live demonstrations will highlight the program. *Information*: Carroll Miller, The College of Agricultural and Environmental Sciences (N), University of California, Davis, CA 95616. Phone: 916/752-6435. *Registration deadline*: 30 July 1985.

Medical and Behavioral Benefits from Primate Research

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Primates share more biological and behavioral characteristics with humans than do other animal species. These striking similarities begin in the basic chemical component of life, the deoxyribonucleic acid (DNA) in human genes. Ninety-eight percent of our DNA can be found in primates. Our genetic relationship to primates, the consequence of our relatively recent common evolutionary ancestry, is manifested in a similarity of development and functioning of the nervous system, particularly the brain, reproductive structures and physiology, cognitive and social behavior, immunological defenses, and other characteristics, some of which are virtually unique to humans and primates.

In the realm of behavior, humans and apes alone seem capable of symbolic referential and linguistic communication. Primates are the species that approximates most closely human maturational and reproductive events. For example, in the great apes, the menstrual cycle is virtually identical to that of human females, and the maturational phase of adrenarche in human males is apparently found only in the apes. Because of great immunological similarities, humans and primates are susceptible to many of the same infectious diseases.

While anthropologists study primates for clues to human origins and nature, psychologists examining social organization and interactions in primates seek to understand principles governing affiliative relationships, sexual behavior, aggression, and other social behaviors. In neurobiology, immunology, pathology, reproductive biology, teratology, neonatology, and cardiology, primates have become critically important and, in some cases, indispensible research models for both understanding basic biological mechanisms and the development and testing of new approaches to diagnosis and treatment.

We present here a sampling of the contributions of primate research to human health and welfare. For reasons of space, not all areas of study are mentioned, but we have attempted to show, through examples, the value and breadth of primate research. For convenience, the term "primate" is used throughout this article to refer only to nonhuman primates.

While the topic of primate conservation is not covered in this article it is a matter of serious concern and deserves mention. The human population explosion and resulting encroachment and destruction of primate habitats in Africa, tropical America and Asia have threatened the future survival of many monkey and ape species in the wild. Primatologists and other research scientists have become increasingly active in primate conservation through the protection of natural habitats and the development of captive breeding programs in this country and abroad, as a societal and scientific obligation.

Atherosclerosis

Until the 1960s, laboratory animals employed in cardiovascular research were primarily rabbits, chickens, dogs, rats, and swine. Primates became major subjects of heart research as a result of studies indicating that atherosclerotic plaques that develop in both monkeys and humans are virtually identical in both gross and microscopic appearance and biochemical composition (13, 14, 137, 138, 139). Primates now are used in cardiovascular studies with the following aims.

1) Identifying the mechanisms of atherosclerotic destruction at cellular and molecular levels (114). Under investigation are the changes that occur in the composition and metabolism of lipoproteins with advancing age and disease.

2) Determining the course and progress of atherosclerotic disease and the way that steps in this process can be interrupted or prevented (142). A recent research focus is the development of asymptomatic lesions in young primates (50) and the role of diet, blood pressure changes, and other factors in the advancement or stabilization of the lesions (83).

3) Defining the relative influence of risk factors (149) (hypertension, diabetes, tobacco, alcohol, gender, fats and other nutrients, obesity and heredity) on disease progression, regression, and prevention.

The importance of dietary lipids and lipoproteins as risk factors has been demonstrated in diet-induced primate models of atherosclerosis (99). Studies also have shown that diets devoid of, or low in, cholesterol can reverse atherosclerosis in monkeys (71, 123). It has been found that plaque produced over a long period is as amenable to regression as plague produced over a short period (99). These and related findings suggest that at all ages humans may reduce risk of heart disease through diet.

The role of exercise in heart disease is also under investigation in primates (114). Research with monkeys exercised on a treadmill indicates that exercise may help reduce the disease and slow the development of plaques even when diet is high in fat (63).

Psychophysiological studies involving blood pressure and cortisol levels (129) are being conducted with primates to determine the role of stress in the development of cardiac disease. Research on monkeys living in stable, as opposed to stressful, social environments indicates that psychosocial stress can act independently of, or

synergistically with, diet and other factors to exacerbate heart disease (70, 119). For example, socially stressed monkeys fed low-fat diets develop more extensive heart disease than comparable groups of unstressed animals. Such studies may explain the occurrence of heart disease in humans with low or normal serum lipids and normal values for other suspected risk factors. Thus, ongoing and future studies should define how social and psychological factors interact with other environmental conditions, drugs, and diet to alter the course of heart disease.

In other primate studies, the amount of dietary cholesterol is varied to induce atherosclerotic lesions which mimic the several levels of disease progression that occur in humans (151). In one study of social groups of monkeys, genetic control of an animal's hyper- or hyporesponsiveness to dietary cholesterol is being evaluated (15). The results may help clarify the role of heredity as a risk or protective risk factor.

Primates are also used in studies of drugs (48) and other agents that change the metabolism of cholesterol. Two agents, cholestyramine (111) and alfalfa seed (71), have been shown to produce regression of the disease in primates fed high cholesterol diets. Possible mechanisms responsible for the regression are being evaluated.

The study of advanced atherosclerosis leading to ischemic heart disease and myocardial infarction (150) is a relatively recent area of primate research involving interventions intended to limit the infarct, reduce the frequency of ventricular fibrillation, and control congestive heart disease (149).

Obesity has long been associated with heart disease, and as a result of primate research a new approach to the control of body weight is being investigated. Studies with monkeys demonstrated that insulin levels in the blood regulate appetite by signaling the brain how fat or thin the body is. It has been known for many years that the amount of insulin secreted from the pancreas is directly proportional to body weight: obese individuals secrete more insulin than do thin people. However, the amount of insulin in the blood does not correlate well with body weight. In primates, it was shown that some of the insulin in the blood enters the cerebrospinal fluid and thereby gains access to the brain. The amount of insulin in the cerebrospinal fluid is directly correlated with body weight. These studies suggest that the amount of insulin secreted per day may modulate food intake to maintain a constant body weight. The clinical use of this feedback system is being evaluated (152).

Aging

The "graying" of the American population and the recognition of the socioeconomic and personal costs of the physical and mental problems of the elderly have focused attention on the need for research on aging. Primates are proving to be important animal models for these studies.

Primates experience many of the age-related changes in mental function, behavior, anatomy, and physiology that humans undergo (88). Learning and memory deficits can be detected in aged primates (4). These animals also have lower levels of certain neurotransmitters, and in the cerebral cortex the capillary walls are thinner, suggesting changes in the blood-brain barrier with age. As primates age, coronary vessels thicken, a common antecedent of atherosclerosis in humans that is often related to the behavioral deficits observed in both aged humans and primates (8).

These and other physical and behavioral similarities between aging humans and primates have been documented in large part by studies at the National Institutes of Health's regional primate research centers. Established in the early 1960s, several centers have colonies of aging rhesus monkeys over 20 years old. One center has a large group of chimpanzees between 45 and 55 years of age. In the wild, these apes rarely live beyond their mid-30s. The research value of these aging primates was emphasized by Dr. Edward Brandt, Assistant Secretary for Health, at a meeting marking the 20th anniversary of the NIH primate research centers program. "As we begin to delve more deeply into the health problems of the aging human, we will be turning more frequently to nonhuman primates for cues. That such research is possible is, to me, one of the greatest accomplishments of this important program" (personal communication, Dr. E. Brandt).

In 1981, one NIH-sponsored primate center launched a 5-year study to determine the impact of diet on biological mechanisms in aging. Two groups, of 36 monkeys each, ranging in age from 4 to 26 years are being studied. This age span is roughly equivalent to 12 to 75 years in the human. One group is fed a semipurified diet high in fats, cholesterol, sugar, and salt; the second is given an alternative diet containing the same number of calories but differing markedly in the proportion of fat to carbohydrate. The alternative diet contains one-sixth the amount of cholesterol, one-fourth the salt, and one-half the sugar of the semipurified diet. Neither diet has alcohol, caffeine, or common food additives or preservatives. Before the study began, base-line data on 48 health indicators were obtained. Periodic checks are documenting how the animals differ as they age and the degree of individual variability within each study group. Under evaluation are the animals' immune and cardiovascular systems, hormonal responses, bone density, neural structure, and social behavior. Researchers also are checking for evidence of atherosclerosis, senile macular degeneration, and periodontal and degenerative bone disorders (112).

In psychopharmacological studies on aging, primates are used to determine the ability of drugs to reduce age-related memory loss. Research has also revealed that aged primates have deficits in memory for recent, but not immediate, events, an increased sensitivity to interfering stimuli, and decreased behavioral flexibility. These changes, which are similar to the behavioral impairments that occur in aged humans, make primates excellent models for studying intellectual and social aspects of aging and attempting experimental interventions and treatments (4).

The role of the brain and hormones in the control of the "hot flashes" and other signs of menopause, a stage in the aging process, is being comparatively studied in postmenopausal monkeys and young ovariectomized monkeys. The development of more effective treatments for the millions of women who suffer menopausal symptoms depends on improved understanding of the underlying mechanisms, which can often be best achieved in animal models (105).

Behavior

Five decades ago, when Dr. Robert M. Yerkes established this country's first institute for primate research, the ability of scientists to correlate observed behavior with physiological activities was extremely limited. Over the past half century, the development of sophisticated methodologies in behavioral and biological measurement now permit a vast array of studies on biological, environmental, and social influences on aggression, dominance-submission, sexual development, mating behavior, maternal-infant relationships, and other primate behaviors.

Endocrine and Seasonality Influences on Reproductive Behavior

Research on primate social behavior has recently focused attention on female sexual maturation, reproductive strategies, infant care, and the influence of social, environmental, and biological factors on reproduction. Results of this research have challenged the assumption that female primates are biologically emancipated from the endocrine influences that govern the reproductive behavior of the majority of mammalian species. Research with groups of rhesus monkeys has correlated female sexual behavior with cyclic hormonal patterns (31) and has demonstrated that the hormonal changes triggering ovulation also initiate a behavioral pattern which signals the male that the female is fertile (31, 143). The female rhesus does not passively attract the male but actively seeks out and initiates sexual activity with males in which she is interested. Female proceptivity, i.e., expression of sexual interest, helps ensure that mating occurs at times of maximal fertility (144). At least one research study indicated that women also may have a midcycle increase in their sexual interest (1).

Besides improving scientific understanding about the roles of the female and the male in rhesus sexual behavior, these studies have provided a model system for evaluating the behavioral and biological effects of hormonal treatments, such as contraceptives and posthysterectomy therapies. In a recent study, an experimental hormonal contraceptive muted the typical midcycle sexual behavioral pattern of female rhesus monkeys living in a social group. Research on the behavioral changes induced by hormonal therapies continues, and the results may indicate that behavioral as well as biological effects of hormone medications should be evaluated by pharmaceutical companies and considered by physicians in prescribing these drugs (143a).

Research on the factors responsible for rhesus monkeys' seasonal fertility patterns, a paradoxical phenomenon for a menstrual primate, may identify new mechanisms that could be used to achieve human fertility control or to correct human infertility. Results of this research should also improve the captive breeding of rhesus monkeys, which no longer are imported from the wild but are important for medical and behavioral research.

Studies of social groups of rhesus monkeys housed in outdoor enclosures have defined the endocrine changes responsible for the onset of the breeding season and its abrupt cessation 5 months later. During the breeding season copulation is generally restricted to the periovulatory period (31, 147). In contrast, rhesus monkeys housed indoors and tested in a pair cage environment typically mate year-round and throughout the menstrual cycle (78), although with a lower frequency during some phases and a clear peak at midcycle. The seasonal pattern of mating that occurs in outdoor social groups of rhesus monkeys, and in primates living in their natural habitats, is illustrated by a study in which the breeding males of the group were vasectomized to prevent pregnancy. The females displayed the same cyclic hormonal and behavioral changes that occurred when they were with fertile males. The females mated with the vasectomized males, but the mating season ended abruptly after 5 months, even though the females were not pregnant.

At one primate research center where breeding seasonality is being investigated, the onset of the rhesus monkey mating season occurs in late summer or early fall, and mating ceases in the spring. As a result, the variation in light cycles that accompany these changes is theorized to be the environmental factor underlying the seasonal mating pattern. The absence of light-cycle variation in indoor housing may explain the year-round mating that occurs under these conditions. The mechanisms by which day length influences ovulatory activity are also being explored. Current research suggests that photoperiod inhibits ovulatory cycles during long days by altering ovarian and pituitary function. To test this hypothesis, the photoperiod is experimentally manipulated (31).

For many decades psychologists have tried to determine how male and female behavioral patterns and psychological traits originate and develop in humans. One theory is that these traits are based on learning and experience (33, 95). Research with primates, however, has shown that sexual differences in anatomy, physiology, and behavior are based substantially on the relative presence or absence of prenatal androgens during a critical period of fetal development. Whereas female characteristics are determined by the prenatal absence of androgens, male characteristics are determined by the prenatal presence of androgens (157).

Experimental manipulation of prenatal androgen levels powerfully influences the kind of typically male or female behavior that develops in primate offspring. Prenatal androgen treatments typically masculinize the external genitalia and impart male psychological traits to genetic rhesus females. These studies indicate that the sociosexual behavior of rhesus monkeys is a product of the interaction of their prenatal endocrinological environment as well as their learning and social experience (34, 95). Besides suggesting possible biological factors that influence human sexual orientation, this research provides basic information about gender development that may be used to derive therapeutic treatments for gender-related problems.

Development of Emotional Expression

The biological and social events that contribute to normal and abnormal behavioral patterns are under intensive study in primates. Research on the effects of varying types and degrees of infant separation from mothers and mother surrogates have documented the importance of emotional care and stimulation for the short- and long-term psychological health of the off-

spring. Research with young primates and observations of orphaned children revealed that nutritional and physical care is not enough. If deprived of emotional nourishment, i.e., attention and expression of affection from the mother or peers, a child or infant primate may not survive or may be impaired both emotionally and in its cognitive development and interaction with social others. Such individuals may be unable to establish normal social relationships and may suffer intellectual impairment as well (60, 90, 135).

For example, a recent study has shown that adolescent monkeys which as infants had experienced separation from their mothers reacted to separation from their peers more negatively than monkeys which had grown up with their mothers. These results indicate that strong emotional nourishment during development improves the individual's ability to cope with subsequent social stress. This work also suggests that since young children react to divorce with varying degrees of depression and other behavioral disturbances, the rising divorce rate may generate an increase in the number of adult cases of depression (61).

Research on depression in young primates has identified short- and long-term physiological changes in heart rate, immune response, sleep patterns, activation of the adrenocortical system, and neurotransmitter synthesis, uptake, and metabolism in the brain (77, 108). These effects resemble the disordered physiology of human affective disorders and provide an opportunity for scientists to understand the psychophysiological concomitants of disease as well as the origins and development of psychosomatic disorders.

Also under investigation are the general physiological mechanisms that contribute to behavioral and life history patterns. Primate species that have different behavioral patterns also differ in the relative balance between the sympathetic and parasympathetic components of their autonomic nervous systems. Similar physiological differences also have been detected in monkeys which belong to the same species but which have different behavioral coping patterns as a result of differing early social experiences (9).

Studies with young monkeys also indicate that genetic factors and predispositions contribute to the development of behavioral problems such as chronic anxiety (134). In one study, monkeys that were separated at the same age from their mothers and lived in identical environments did not respond similarly to novel situations or to normal day-to-day experiences. Abnormal behavior such as timidity and anxiety was observed in some animals. An investigation of the percentage of these timid and anxious young monkeys found common paternal or maternal lines (133). The possibility of a genetic predisposition to be timid and anxious is being explored.

A primate model has recently been developed for chemically induced anxiety by the injection of a β-carboline derivative. Within minutes following injection, monkeys displayed physiological and behavioral signs of anxiety. Primate research on the neurochemical basis for anxiety may help improve pharmacological and other treatments for chronic anxiety which affects 10 million persons in the United States so severely that they seek professional help (80, 84, 136).

Many primate studies focus on the physiological and chemical mechanisms in the brain's response to drugs. New pharmacological compounds designed to treat human behavioral disorders are screened in primate models. A relatively new area of drug research involves the effects on the social organization of primate groups of drugs that humans may abuse. The results indicate that social factors such as dominance rank or position mediate the behavioral effects of psychoactive drugs (127).

Aggression and violence play major roles in both human and primate societies. Through research on social living groups of primates, scientists hope to identify the mechanisms responsible for the control and expression of aggression. Much of this research has been conducted with rhesus monkeys. Although adult rhesus are capable of inflicting lethal wounds, the agonistic encounters of these monkeys are rarely fatal because their aggression is typically characterized by noncontact forms of expression (5–7). According to a current study, this behavioral pattern, which minimizes the disruption of the social group, must be learned by young rhesus males. In one study, the socialization of young rhesus males is monitored in a social group with adult males and females and juveniles of both sexes and a group in which the adult males have been removed. If the adult males are the socializing agents, as they are theorized to be, the young males in the second group will grow to adulthood using biting and other contact forms of expression much more frequently than their counterparts in the first group. The results of this research may provide a new approach to the understanding of the origins of aggressive behavior in human society (154). This research may reveal that the psychological health and coping ability of males can be greatly influenced by an adult male role model during childhood.

Another influence on the way that rhesus monkeys handle conflict is the dominance hierarchy. Many primate species live in groups whose social structure is based on dominance-submission relationships, a pecking order that is generally nonlinear and highly complex. When two monkeys want the same object, the lower-ranking animal typically submits rather than fight with the higher-ranking animal and its allies. Comparative studies of humans and primates indicate the importance of learning and social context in dominance-submission relationships. In primate groups, dominance rank is based primarily on social skills, alliances, and other behavioral patterns that are inherited or acquired through learning from the mother. Dominance rank is not permanent; it can change when an animal joins a group, a death occurs, new alliances are formed, or for unknown reasons. The results of such studies with primates have obvious relevance for the development of hypotheses about the nature and origins of human social interactions (6).

Research on dominance relationships in primates and other animals has influenced several psychologists to study peer relationships among children and adults. One group of psychologists studied a group of preschoolers and identified a dominance hierarchy in terms of "attacks" and "retreats" and found that 76% of the "property fights" among these children could have been predicted by the status of the children involved (132). These comparative studies indicate that humans who work, live, or socialize in small stable groups sort one another out in a hierarchial pattern which clearly influences the behavior of the group and its members.

Communication

Beginning with Dr. Robert M. Yerkes' pioneering studies (155) in the 1920s, psychologists have been probing the mental capacities of primates in order to understand their intelligence, perception, and communicative abilities. The results of this research improve our understanding of the cognitive abilities of primates and the origins of human language and intelligence.

Among the most exciting approaches to primate cognition are the several studies on the ability of chimpanzees and other apes to learn and use language. Because primates do not have the neural and vocal apparatus required for human speech, ape communication studies use an artificial language—American Sign Language (22, 29, 89), manipulatable plastic symbols (93), or geometric symbols on a computer-operated keyboard (115).

These studies have demonstrated that apes can develop large vocabularies and make novel uses of their language. In one study, two subadult chimpanzees use symbols not only to communicate with each other but also to refer to objects, people, and events not immediately present. Referential communication, the accrual of meaning to arbitrary symbols so that they represent the actual referents in communication, is regarded as a key characteristic of human semantics (118).

Although apes have not evolved cognitively to a degree that ensures spontaneous development or acquisition of language, with concerted effort certain aspects of language can be taught to them. As a result, apes are useful and unique models for studies on the evolutionary conditions under which language may have emerged in humans (116).

Research on the apes' communicative abilities has also provided a practical benefit to human society. A new approach has been developed for teaching language to human children who, because of severe mental retardation, cannot learn language as normal children do. The computer-operated keyboard and lexigram system of symbols that were developed with apes have been used in the teaching of language to these handicapped young people. This system has enabled individuals who were previously without language to interact with others and, as a new experience in their lives, be able to express their thoughts, feelings, and needs and to understand and respond linguistically to their parents and teachers. With further refinement, this new instructional method and communication system may be used in schools and homes of the retarded (113).

A recent demonstration of the way in which monkeys communicate with each other about external objects and events in their environment came from a study of vervet monkey troops in the wild. Tape recordings were made of the troops' alarm calls in response to specific predators, i.e., pythons, leopards, and martial eagles. The group's behavior also was documented. When the audiotapes were played back to other groups of vervet monkeys, the animals behaved as if the specific predator was there. For example, when the tape recording of the alarm call for an eagle predator was played, the vervet monkeys looked up into the sky and took cover under a bush. When the alarm call for snake predator was played, the animals responded by looking at the ground and climbing a tree. Analysis of the primates' calls on the sound spectrograph revealed distinct patterns associated with specific behaviors. Thus, the components of primate vocalizations may function similarly to words of human language (124). By studying the vocalizations of primates, information may be obtained that could improve our understanding of the origins of human language.

Infectious Diseases

The understanding and control of many infectious diseases such as poliomyelitis, yellow fever (18), measles (56), rubella (47) and hepatitis B have depended on research with primates. Unconventional infectious agents known as slow viruses have been identified in primate studies (27). Because of the striking immunological similarities to humans, primates may prove to be the only laboratory animals susceptible to acquired immune deficiency syndrome (AIDS).

Slow Viruses

Chimpanzees were critical for Gadjudsek's discovery that a slow virus must be the infectious agent of kuru, a fatal brain disorder affecting a New Guinea tribe. Several laboratory animal species were inoculated intracerebrally with brain material from deceased kuru victims, but only chimpanzees proved susceptible (28). Since 1975, when Gadjudsek received a Nobel Prize in Medicine, other primate species have been infected with the kuru slow virus. Primates also are involved in research on the possible role of slow viruses in AIDS, Alzheimer's disease, and other degenerative disorders.

One likely candidate for the slow virus group is the JC virus, which induces brain tumors in owl monkeys and squirrel monkeys. These animals are under investigation as a model for virus-induced human brain tumors. Results of this research may contribute to the diagnosis and treatment of certain human brain tumors (96).

Polio

The conquest of polio began in 1909, when Landsteiner and Popper demonstrated that poliomyelitis could be transmitted from humans to apes and monkeys (65). Primates became a key animal model for studies on the pathogenesis of polio and for vaccine development when it was recognized that among animal species only primates could contract human poliomyelitis. Using monkeys as test subjects in 1953, Salk developed the killed polio vaccine used in many countries today; and in 1959, Sabin developed the live attenuated vaccine currently used in the United States.

The health impact of the polio vaccine has been dramatic. In the peak year of the polio outbreak during the 1950s, there were ~50,000 cases of the disease. Many victims died or were permanently crippled. In 1982, only seven cases of polio were reported in the United States. Primates still play a role in the conquest of polio in the production and efficacy and safety testing of vaccine before it is released for human use (91). The importance of safety testing was emphasized in a 1982 World Health Organization publication which referred to the disastrous effects that would result "if a batch of live polio vaccine were to be released without being fully tested in nonhuman primates . . . . Vaccines are given to young healthy infants, often in mass campaigns before the danger is recognized. Safety testing in animals is humanity's only guard against such potential disasters" (153).

Yellow Fever

Research with primates clarified the difference between the urban and jungle types of yellow fever, and studies of the disease in monkeys led to the production of the first yellow fever vaccine (17). Because South American monkeys are the major reservoir of yellow fever in the New World, the health of these monkeys is monitored in the wild as part of public health surveillance (81).

Hepatitis B

Hepatitis B is a viral disease that annually afflicts 200,000 persons in the United States alone. There are ~200 million carriers of hepatitis B worldwide. At least 3 million infants born in southeast Asia alone will acquire the infection at birth. Many will become carriers and develop severe liver damage including liver cancer (55). In 1981, the US Food and Drug Administration approved the world's first hepatitis B vaccine (74). This major advance depended on research with chimpanzees and other primates, since hepatitis B cannot be transmitted to other laboratory animals, and until recently, the viral agents which transmit hepatitis could not be successfully cultivated in vitro. Marmosets and chimpanzees currently are being used to study hepatitis A and hepatitis non-A, non-B (10, 17, 106).

Malaria

Primate studies on the pathogenesis of malaria showed that all four species of human malaria pathogens have a fourth, or liver, stage which can remain asymptomatic indefinitely until the parasites are released into the blood stream. It is then that relapses of malaria occur (156).

Potential treatments against malaria, a disease that affects 200 million people worldwide, have been tested in primates. Vaccine development and testing are the current focus of malaria research as a result of the development of malaria-bearing mosquitoes resistant to insecticides and the appearance of drug-resistant malarial parasites. In one study, chimpanzees are inoculated with human blood containing different species of the *Plasmodium* parasites. The parasites from the chimpanzees' blood are used in the development of monoclonal antibodies that may be the major component of a malaria vaccine (94, 153).

Yersiniosis and Filariasis

Yersiniosis, an increasingly common infectious bacterial disease of humans, is being studied in monkeys in which the clinical and pathological features of the disease are comparable to that in humans. These primates are being used to study the epidemiology, pathogenesis, and pathogenicity of various *Yersinia* species and serotypes, particularly the so-called environmental strains of the bacillus. The spontaneous occurrence of a significant number of yersiniosis cases in primates also provides the opportunity to evaluate postinfection disorders, the most notable being reactive arthritis and amyloidosis (75).

Primates also are involved in studies on a variety of tropical diseases. Filariasis, for example, is one of the world's six most important tropical diseases as classified by the World Health Organization. Between 250 and 300 million people worldwide are afflicted with the parasites which are transmitted by blood-sucking insects and are responsible for diseases such as elephantiasis and onchocerciasis ("river blindness"). Primate studies may contribute to effective chemotherapeutic agents that can eradicate the parasites in the human population (11).

Leprosy

In 1982, the World Health Organization issued a warning that leprosy, which afflicts 15 million people worldwide, may increase in incidence as a result of the bacillus becoming resistant to dapsone, the most effective and inexpensive drug for the disease (67). A vaccine and new effective treatments are urgently needed and may be expedited by research with sooty mangabey monkeys that have been infected with leprosy. This primate model, the first for leprosy research, is based on the discovery in 1979 of a sooty mangabey infected with naturally occurring lepromatous leprosy, the most severe form of the disease. The monkey's illness advanced through stages almost identical to those occurring in human lepromatous leprosy. The disease was transmitted from this animal to other sooty mangabeys, and this species also proved vulnerable to transmission of leprosy from humans. It is a distinct research advantage that leprosy develops swiftly in the monkeys. Some have developed signs of the disease less than 6 months after inoculation. In humans, the incubation period can take many years (25).

Acquired Immune Deficiency Syndrome

Research with chimpanzees may prove to be one of the keys to understanding AIDS and developing treatments and a vaccine against the disease. Three scientific institutions have inoculated chimpanzees with the LAV and HTLV-3 retroviruses, the suspected infectious agents of AIDS, or with blood and other material from AIDS patients. Four months after inoculation with LAV virus, two chimpanzees developed antibodies against the virus and evidence of AIDS infection in viral isolation studies. In another study, two chimpanzees that received transfusions of human plasma from a patient with lymphadenopathy syndrome, a condition believed to be an early form of AIDS, showed evidence of infection with the HTLV-3 virus. The chimpanzee is thus far the only laboratory animal that has proved susceptible to the AIDS infectious agents (76, 121).

In addition, monkeys of the macaque species at two NIH primate research centers have developed a disorder that may be akin, but not identical, to AIDS in humans. The primate version, called simian acquired immunodeficiency syndrome (SAIDS), is characterized by severe immunosuppression, inflamed lymph glands, lymphoma, excessive weight loss, anemia, fever, diarrhea, and central nervous system disorders. It is a severe and usually fatal disease of macaques. A new type D retrovirus was detected in both groups of monkeys (19, 72, 73). Studies of SAIDS can contribute to our knowledge of human AIDS and other immunological disorders and possible methods of diagnosis and control.

Cancer

For decades it has been theorized that some human cancers arise from a disruption of the body's immune system or DNA replication of body cells by an infectious agent, either acting alone or in unison with other factors. Although conclusive proof of a connection between an infectious agent and cancer has not yet been found in humans, some intriguing evidence for its existence was discovered in research with primates. In studies with

kidney cell cultures from squirrel monkeys, in a project unrelated to cancer virology, a herpesvirus was detected and isolated. The oncogenic properties of this new virus were demonstrated in subsequent studies in which marmosets and owl monkeys inoculated with the herpesvirus developed leukemia. Named *Herpesvirus saimiri*, this was the first herpesvirus proven oncogenic in primates and other mammals as well (49).

Herpesvirus saimiri, however, was not the first herpesvirus linked to cancer. In the early 1960s, when Burkett defined the human malignancy which today bears his name, Burkett's lymphoma, he suggested an infectious basis for this particular form of cancer. Studies by Epstein and his associates reported in 1964, uncovered the now-called Epstein-Barr herpesvirus (EBV). Although EBV has not yet been proven to cause human Burkett's lymphoma, cotton-topped marmosets and owl monkeys inoculated with EBV developed lymphomas (17, 49). The marmosets are being used by Epstein to test an experimental vaccine against EBV (82).

In the early 1970s, another herpesvirus was identified in primates. Named *Herpesvirus ateles*, this agent can induce malignant lymphoma in cotton-topped marmosets (49).

Endogenous infectious agents have been the focus of much research attention since the discovery of type C virus particles in the placentas of humans and primates. Type C viruses have been isolated from baboon tissue (41), and in studies with primates, various forms of this virus (Rouse sarcoma virus, feline sarcoma virus, and simian sarcoma virus) have been identified and found reproducibly tumorigenic in primates (107).

Chimpanzees are used in the development of monoclonal antibodies against certain forms of cancer, primarily those that arise from solid tumors. Because of the immunological similarities between humans and chimpanzees, monoclonal antibodies derived from chimpanzee material should be highly specific when used in laboratory diagnostic assay and may be found safe and effective when used in human treatment. The safety and effectiveness of murine monoclonal antibodies also are being tested in monkeys (42, 126).

The Brain

Primates are used by psychologists, anatomists, and physiologists to trace the development of memory and its intricate pathways in the brain (44), as well as to study motivational states such as hunger, thirst, sexual behavior, and emotion in relation to brain structures and their chemistry (117). Research on the primate brain at all life stages, from infancy to old age, is helping to explain the physiological basis of vision (140). There are several ongoing studies of the brain areas responsible for producing and using neurotransmitters that have been implicated in certain central nervous system degenerative diseases and behavioral pathologies (30, 84). Primates are often the final animal model for the development and testing of procedures and drugs that if proved safe and effective, can be applied to the treatment of human central nervous system disorders such as epilepsy and Parkinson's disease (68).

Vision

One of the most recent contributions of primate research to human clinical treatment has been the studies of Hubel and Wiesel (146). For more than 16 years, they studied the development and functioning of the visual system in monkeys and cats. The results of their research revealed that monkeys, and by implication humans, are not born with a fully developed visual cortex. The maturation of the connections between cells and the cells themselves depends on visual stimulation. If deprived of stimulation, as when an eyelid is occluded experimentally in a monkey or vision is impaired by a cataract in a child, changes occur in visual neurons in the brain and their connections. These abnormalities can seriously affect visual functioning. In contrast, the same type of visual deprivation did not affect the cortical cells of adult monkeys, apparently because they had passed the critical period of visual development.

The primate studies of Hubel and Wiesel also provided important information about the mechanisms of visual development, plasticity of the visual cortex, and the processes that govern the balance between different visual inputs which permit the cerebral cortex to integrate information. Competition and synchronization of inputs are important factors in forming and maintaining this balance. If these processes are disturbed early in life, the visual system may be permanently altered.

The studies for which Hubel and Wiesel received the Nobel Prize underlie the current emphasis on early diagnosis and treatment of human infants with eye disorders. However, the ideal age for treatment and the most effective therapies for congenital eye disorders are unknown and may eventually be determined, in a large degree, by current studies (personal communication, A. Gammon, Yerkes Primate Research Center, Emory University) with young primates. For example, postlensectomy treatment for congenital cataracts, one of the three leading causes of blindness in children, is under investigation at one of the NIH-sponsored primate centers. One experimental treatment involves the application of recently developed continuous-wear contact lenses, which are worn by young monkeys following lens removal, which is the equivalent of cataract surgery in children. Acuity and other visual capacities are measured to assess the efficacy and safety of different designs of continuous-wear contact lenses. Such lenses should prove an asset for very young children, in whom constant lens changing can be a difficult problem.

The development and evaluation of intraocular and intracorneal lenses for patients who have had cataract removals are also being conducted with primates (109). Within several years, these lenses will probably contain ultraviolet radiation-filtering agents because of primate studies showing that removal of the natural lens in cataract surgery leaves the retina vulnerable to damage from ultraviolet radiation (104). Other human visual disorders whose prevention and treatment are being studied in primates include uveitis, astigmatism resulting from corneal graft surgery, glaucoma, ocular hypertension, and presbyopia.

Split Brain

Primates were involved in the split brain studies of Sperry (128), who shared the 1981 Nobel Prize with Hubel and Wiesel. Sperry's studies with cats, primates, and human patients who had undergone commissurotomy for intractable epilepsy challenged the view of a subordinate, or minor, nonlanguage right hemisphere in

contrast to a supposedly more highly evolved and intellectual left hemisphere. Sperry's animal work predicted in part the findings in humans that left-right hemisphere cognitive differences are subtle and qualitative and that each disconnected hemisphere behaves as if it is not conscious of cognitive events in the partner hemisphere. Each brain half, therefore, has its own largely separate cognitive domain with its own perception, learning, and memory experiences.

Movement Disorders

Primates are also employed to evaluate the structure and function of pathways known to participate in motor activities and to define the anatomical and biochemical relationships between the brain stem and the higher centers and their role in movement disorders. Experimental brain lesions have been used to produce a Parkinsonian tremor and to isolate and define components of the motor system which are involved in this disease and others which impair motor activity. Scientists have determined with primate and other animal models that central feedback loops play important roles in the control of movement and that abnormalities in these loops are responsible for certain tremor disorders. A primate model of tardive dyskinesia in humans also has been developed in primates by the chronic administration of haloperidol, believed to block dopaminergic transmission and to affect the cerebellar pathways (51).

Alzheimer's and Parkinson's Diseases

Primates also are used in studies on Alzheimer's disease, a devastating and irreversible form of dementia that affects 5% of the population over the age of 65 and half of those over 80. To a lesser degree younger people are also afflicted. Studies with primates and other laboratory animals have implicated the nucleus basalis of Meynert as the brain region that is critical in the development of Alzheimer's disease (58). Autopsy findings on Alzheimer's patients confirmed the animal studies and showed that ~75% of the neurons of the nucleus basalis are lost in patients with the disease (145).

Primate research also has explained a pathological feature of Alzheimer's: the abundance of neuritic plaques or clusters of nerve endings surrounding a core of extracellular amyloid, in the cerebral cortex. Primate studies have revealed that these plaques consist partly of degenerating cholinergic axons arising from the nucleus basalis. By lesioning the basal forebrain cells of monkeys and evaluating the chemical and anatomical alterations, scientists are attempting to simulate the pathogenesis of Alzheimer's disease.

In 1981, the first animal model for research on Parkinson's disease was developed through the chronic administration of the chemical MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). This compound produces many of the clinical and physiological features of human Parkinson's disease, including the loss of dopamine-producing brain cells. Primates injected with this substance are being used to test the safety and efficacy of surgical transplants of donor dopamine-producing tissue, such as adrenal medulla tissue or fetal substantia nigra tissue. The primate model for Parkinson's disease is also being used to investigate the disorder's "on-off" effects and to test experimental drugs (68).

Reproduction

Today, many primate species are endangered in their natural habitats because of the ever-increasing demand for land and raw materials created by the human population explosion. Basic research on primate reproductive biology in the interest of both humans and the primates is urgent. The development and testing of improved fertility control methods depend to a significant extent on the results of research on the reproductive functioning of primates as models for humans (39). Laboratory and field studies on primate reproductive biology and behavior provide information needed for zoos and research centers to design captive breeding programs. Captive propagation and conservation of natural habitats will also help prevent the extinction of these animals.

Basic reproductive research with primates is focused on areas such as hormonal and other biological mechanisms responsible for ovulation, steroid feedback events governing gonadotropin secretion (53), adrenarche, puberty, and adolescence (35), sperm maturation and transport (53), embryonic and fetal development (46), fetal exemption from the maternal immune response, and the onset of labor (21). Results of these basic research studies are applied to clinical areas such as fertility control (39), correction of infertility (97), teratologic testing, in vitro fertilization, and embryo transfer, correction of fetal disorders in utero (45), prevention of asphyxia in newborns (personal communication, Dr. A. Patterson, Yerkes Primate Research Center, Emory University), treatment of premature labor (110), hyaline membrane disease (101), and respiratory distress syndrome (52, 148).

Fertility Control

Several new approaches to female fertility control currently being tested in primates include nasal spray compounds (64), active and passive immunization against either the β-subunit of human chorionic gonadotropin, luteinizing releasing hormone, zona antigens, or epididymal fluid proteins (39, 40, 130), steroidal anti-implantation agents (39), novel steroid combinations, and nonhormonal cervical mucus modifiers (32, 86).

While antiandrogens (92), gossypol (125), and other potential contraceptive agents for human males are being investigated in primates, the ideal male birth control method may depend on the results of current research on the basic mechanisms of spermatogenesis. These studies may identify the steps in the male reproductive process that can be safely and effectively interrupted for long-term reversible fertility control (39).

Without similar basic research studies, the female fertility control methods that are currently used or under study could not have been developed. The experimental nasal spray contraceptives are based on research first conducted in lactating rats and then monkeys, demonstrating that amenorrhea can be significantly extended by increasing endogenous prolactin secretion. Primates were later used to test the intranasal route of steroid administration as a way to deliver minimal, but effective, concentrations of steroids that boost endogenous serum prolactin levels. Preliminary studies indicated that the steroids enter the cerebrospinal fluid when sprayed intranasally and the dosage required is less than that needed to block ovulation by conventional routes of drug administration (64).

Basic research also underlies a new nonhormonal approach to fertility control based on the monthly cyclic changes that characterize both human and primate cervical mucus. During much of the cycle, these secretions are an effective block to sperm transport. At midcycle, the structure and chemical nature of these secretions change in a manner that permits the passage of sperm into the reproductive tract. A method for the manipulation of cervical mucus secretions so that they continuously block sperm passage has been achieved in primates. However, the delivery system for the chemicals known to maintain this state remains to be developed. Although the human application of this new and unique fertility control method is still to occur, the same approach to cervical mucus manipulation is now being used to achieve fertility in women, who for a variety of reasons, have cervical mucus which blocks the passage of sperm even at midcycle (32, 86).

Studies of the neuroendocrine system of primates should identify causes and ways of correcting infertility. For example, research on the role of gonadotropin in stimulating ovulation in primates has revealed that this hormone is not secreted steadily but is released in bursts of approximately one per hour. A treatment regimen which mimics secretory pattern will induce ovulation in monkeys that have not ovulated. Based on this research, portable minipumps that are implanted under the skin to administer the hormone at regular intervals are being used in the treatment of human infertility (79, 97).

In Vitro Fertilization

As a solution to female infertility caused by impaired fallopian tubes, in vitro fertilization has received great public attention. Extensive in vitro fertilization research with primates followed the first birth of a human from a laboratory fertilized egg. Several scientific laboratories are studying in vitro fertilization in the chimpanzee, rhesus monkey, baboon, and squirrel monkey (21). Pregnancies have resulted from in vitro fertilization in the rhesus and the baboon, and the offspring were born to surrogate mothers (24, 120). These various in vitro fertilization studies should improve the technique so that it will have a higher frequency of success in humans. Primate models for in vitro fertilization will also be used to study the developing embryo and evaluate the effects of drugs and other environmental agents on the embryo and the processes of cellular differentiation (102). These are areas in which research is badly needed and cannot be conducted in human embryos.

Alternatives to in vitro fertilization have been developed in primate research studies. These include low tubal transfer of eggs which are collected before ovulation and placed back into the fallopian tube below the point of blockage and surrogate embryo transfer in which the embryo is taken from the donor and transferred to the reproductive tract of the infertile female. Low tubal transfer can benefit women who have partially normal fallopian tubes, and surrogate embryo transfer is designed for women without ovaries and tubes (103).

Pregnancy and Development

Pregnancy and fetal development are studied in primates, since they rarely can be investigated directly in humans. Because their placentas are as permeable to glucocorticoids as those of humans (85), primates are models for fetal and neonatal respiratory distress syndrome, the dynamics of amniotic fluid, and the possibly beneficial effects of glucocorticoids. These and other structural and functional similarities to humans make primates invaluable in research on the regulation of uteroplacental blood flow and the use of amniotic fluid sampling as an index of the hormonal milieu of the fetus. Primates are also being studied to determine the relative roles of maternal, placental, and fetal hormones on the progress and outcome of fetal hypothalamopituitary-gonadal development (46). The results of these studies will provide important information about fetal development and the role of prenatal influences on gender, reproductive development, and sexual behavior.

Fetal-placental and maternal interactions leading to parturition in primates are being examined in order to identify the factors governing the onset of labor in humans and the mechanisms responsible for premature labor (21). A serious problem that can occur during birth is asphyxia. The results of current studies on oxygen deprivation in fetal monkeys can improve the detection, prevention, and treatment of asphyxia and related human disorders, which include cerebral palsy (personal communication, Dr. A. Patterson, Yerkes Primate Research Center, Emory University).

Studies with primates also provide relevant information about the processes that initiate and govern the maturation of the reproductive endocrine system from early fetal life through puberty. Of particular interest is adrenarche, the human prepubertal stage characterized by activation of the adrenal cortex. Research with apes, the only animals in which adrenarche is known to occur, should contribute to our scientific understanding of normal sexual maturation and mechanisms responsible for abnormal sexual development (35).

Teratology

Teratological studies often involve monkeys, particularly if the test agent has low levels of teratogenicity in common laboratory animals such as rodents, has unique properties which indicate that additional evaluation is needed, or may be used during pregnancy or before pregnancy is recognized (141). Although experimental studies in mammalian teratology began in the 1920s, it was not until the thalidomide tragedy of the late 1950s and early 1960s that the value of proper teratological screening was widely realized. If thalidomide had been properly tested in pregnant monkeys, its potential for causing limb and other deformities in the fetus would have been recognized at once, and it probably would never have been given to pregnant human females (20, 43).

Intrauterine Surgery

As a result of primate research, medical science has embarked on a new frontier—the diagnosis and correction of hydrocephalus and other neural tube disorders in the fetus. Techniques for intrauterine surgery for humans were developed in pregnant monkeys, and the success of these studies now enables clinicians to correct hydrocephalus in utero, so that human infants will have a chance for a normal life. Primates also are models for intrauterine correction of spina bifida and encephaloceles (38, 45, 59).

Respiratory Distress Syndrome

To prevent respiratory distress syndrome in premature infants, physicians administer corticosteroid hormones prenatally to the mother. Research with primates sug-

gests that the dosages currently used in human treatment may not be sufficient to stimulate complete maturation of the human fetal lung. Other primate studies have shown that dexamethasone, a corticosteroid, can produce severe brain changes in fetal rhesus monkeys whose mothers were given various dosages of the drug late in gestation. The neurological changes in treated fetuses are being investigated, and the results should provide information guidelines for clinical use of dexamethasone in human patients (148).

Surgery and Dentistry

In 1981, a middle-aged woman dying from cardiopulmonary hypertension underwent a heart and lung transplant. The operation, the first of its kind on a human patient, was a success. Since then, other patients have received heart and lung transplants, which were tested in primates prior to their application in humans.

With the development of drugs and other treatments to prevent or reduce graft-vs.-host disease, the number of organ transplant surgeries is expected to increase. Primates are being used to evaluate possible approaches to immunosuppression of organ transplants. These include lymphoid irradiation (37), platelet transfusions (87), and injections of monoclonal antibodies directed against antigens expressed on subsets of lymphocytes (3). The results of primate studies with monoclonal antibodies are promising. For example, a monoclonal antibody directed against an antigen (T3) common to all peripheral T-lymphocytes can reverse acute graft rejection in monkeys with kidney transplants. Monoclonal antibody treatment effectively removed T3 positive cells from the animals' circulation. When monoclonal antibodies against T4 cells were injected into monkeys, T4 positive cells decreased significantly in the circulation and kidney graft survival improved (54).

Experimental ophthalmic surgery also uses primates. Epikeratophakia, the insertion of donor corneas into the eyes of human cataract patients, was refined in research on several monkey species. The implanted corneas become living contact lenses. Monkeys also are used in the development and testing of refractive keratoplasty, in which a hydrogel lens is implanted within the layers of the cornea to alter its curvature and improve the vision of cataract patients who have had the natural lens removed. Although human corneas are the preferred biological implant, they are not as widely available as hydrogel lenses and cannot be as easily cut and custom-sized for the patient (personal communication, Dr. B. McCarey, Yerkes Primate Research Center, Emory University).

Studies also have been conducted in primates to determine the optimum extent and the proper timing of vitrectomy in the treatment of penetrating injuries in the posterior area of the eye (36, 158). In addition, primates were used to evaluate laser surgery for repairing and restoring function to damaged nerves (26).

Dental research uses primates to develop and test new surgical approaches and ways of preventing and treating disease. Synthetic dental implants that serve as anchors for removable dentures and fixed teeth were tested and shown safe and effective in primates (122). Primates also are involved in the development and testing of artificial tooth implants (personal communication, Dr. M. Spector, Yerkes Primate Research Center, Emory University) and are used in research on the effects of immunoregulating drugs (62) on periodontal disease and subgingival microflora, various vaccine preparations to prevent caries caused by streptococcus mutants (66), and vitamin C (2) as a preventive and treatment for root surface caries and periodontal disease.

Environmental Health

Primates are used to assess the health consequences to humans exposed to various environmental agents such as ozone. Low levels of ozone, the most damaging pollutant in photochemical smog, caused slight but obvious damage to the small airways of the lungs of three species of monkeys. Exposure to large amounts of ozone caused lung inflammation and fibrosis and immunological changes that can increase allergic reactions and asthma-related problems.

Studies with monkeys also have shown that the cells lining the lung can adapt to low concentrations of ozone. Long-term research is being conducted on ozone exposure to determine the relationship between the ongoing rate of damage and cumulative damage at various intervals of exposure. The research results should help establish safe air-quality standards and help clinicians devise therapies to evaluate and reverse the effects of smog (12, 69).

Both humans and animals have been accidentally poisoned by polychlorinated biphenyls (PCBs) and Dioxin. Although PCBs are no longer manufactured in the United States, they were used for decades as heat-transfer agents and insulators in electrical equipment. They are widespread in the environment also, because disposal practices for PCBs were often careless. The highly toxic and carcinogenic Dioxins are still entering the environment as contaminants in pesticides and herbicides and in the effluents from municipal incinerators.

Exposure to PCBs and Dioxins produces similar effects in humans and primates. Therefore, monkeys are being used to study the effects of these agents and the mechanisms of their toxicity. More information about the storage and metabolism of PCBs and Dioxin is necessary in order to develop appropriate therapy for those who are poisoned (98).

As a result of medical and public concern, a 6-year study was conducted on the effects of microwave radiation. No cataracts or other harmful health effects were evident in the monkeys exposed to intermittent intense microwaves of a 10,000-MHz frequency. The results of this study are important because many persons are exposed to microwave and lower frequency radiation (100).

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References

1. Adams, D. B., A. R. Gould, and A. D. Burt. Rise in female initiated sexual activity at ovulation and its suppression by oral contraceptives. *N. Engl. J. Med.* 299: 1145-1150, 1978.

2. *Atlanta Constitution, The.* Study says vitamin C curbs two oral diseases. Atlanta, GA, 1983, March, sect. A: 3.

3. Balner, H., and M. Jonker. In vitro and in vivo effects in rhesus monkeys of monoclonal antibodies against human and monkey T-cell subsets. *Eur. Surg. Res.* 14: 447-463, 1982.

4. Bartus, R. T., R. L. Dean, and B. Beer. An evaluation of drugs for improving memory in aged monkeys: implications for clinical trials in humans. *Psychopharmacol. Bull.* 19: 168-184, 1983.

5. Bernstein, I., and T. P. Gordon. The function of aggression in primate societies. *Am. Sci.* 62: 304–311, 1974.

6. Bernstein, I., and T. P. Gordon. The social component of dominance relationships in rhesus monkeys (*Macaca mulatta*). *Anim. Behav.* 28: 1033–1039, 1980.

7. Bernstein, I., L. Williams, and M. Ramsay. The expression of aggression in Old World monkeys. *Int. J. Primatol.* 4: 113–125, 1983.

8. Bowden, D. (Editor). *Aging in Nonhuman Primates.* New York: Van Nostrand Reinhold, 1979.

9. Bower, B. Monkeying with stress. *Sci. News* 125: 234–235, 1984.

10. Bradley, D. W., J. E. Maynard, K. A. McCaustland, B. L. Murphy, E. H. Cook, and J. W. Ebert. Non-A, non-B hepatitis in chimpanzees. Inference with acute hepatitis A virus and chronic hepatitis B virus infections. *J. Med. Virol.* 11: 207–213, 1983.

11. Brown, F. Filiarsis. *Tulane Med.* 14: 4, 1983.

12. Castleman, W., J. Gillespie, P. Kosch, L. Schwaitz, and W. Tyler. The role of nonhuman primates in environmental pollution research. In: *Assessing Toxic Effects of Environmental Pollutants*, edited by S. D. Lee and J. B. Mudd. Ann Arbor, MI: Ann Arbor Science Publishers, 1979, pp. 15–30.

13. Clarkson, T. B. Symposium summary. In: *The Use of Nonhuman Primates in Cardiovascular Diseases*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980, p. 452.

14. Clarkson, T. B., H. B. Lofland, B. C. Bullock, N. D. M. Lehner, R. St. Clair, and R. W. Prichard. Atherosclerosis in some species of New World monkeys. *Ann. NY Acad. Sci.* 162: 103, 1969.

15. Clarkson, T. B., R. W. Prichard, B. C. Bullock, N. D. M. Lehner, H. B. Lofland, and R. St. Clair. Animal models of atherosclerosis. In: *Animal Models for Biomedical Research III.* Washington, DC: Nat. Acad. Sci., 1970, pp. 22–41.

16. Cowan, R. Rhesus monkeys provide model for symptoms of menopause. *Res. Resour. Rep.* 7(11): 1–3, 1983.

17. Daniel, M. D., N. W. King, and R. D. Hunt. Nonhuman primates as models for human viral diseases. In: *Nonhuman Primate Models for Human Disease*, edited by W. R. Dukelow. Boca Raton, FL: CRC Press, 1983, pp. 55–56.

18. Daniel, M. D., N. W. King, and R. D. Hunt. Nonhuman primates as models for human viral disease. In: *Nonhuman Primate Models for Human Disease*, edited by W. R. Dukelow. Boca Raton, FL: CRC Press, 1983, pp. 66–68.

19. Daniel, M. D., N. W. King, N. L. Letvin, R. D. Hunt, P. K. Sehgal, and R. C. Desrosiers. A new type D retrovirus isolated from macaques with an immunodeficiency syndrome. *Science* 223: 602–605, 1984.

20. Delahunt, C. S., and L. J. Lassen. Thalidomide syndrome in monkeys. *Science* 146: 1300–1305, 1964.

21. Dukelow, W. R. The nonhuman primate as a reproductive model for man. In: *Nonhuman Primate Models for Human Disease*, edited by W. R. Dukelow. Boca Raton, FL: CRC Press, 1983, pp. 79–105.

22. Fouts, R. S. The use of guidance in teaching sign language to a chimpanzee. *J. Comp. Physiol. Psychol.* 80: 515–522, 1972.

23. Fox, J. L. Memories are made of this. *Science* 222: 1318, 1983.

24. Freiherr, G. Fertilization of monkeys to allow testing of human birth defects theory. *Res. Resour. Rep.* 8(6): 1–6, 1984.

25. Freiherr, G. Monkeys with leprosy: models for studying an ancient disease. *Res. Resour. Rep.* 7(7): 1–7, 1983.

26. Freiherr, G. Laser surgery mends nerves. *Res. Resour. Rep.* 6(12): 1–5, 1982.

27. Gajdusek, D. C., C. J. Gibbs, Jr., and M. Alpers. Experimental transmission of kuru-like syndrome to chimpanzees. *Nature London* 209: 794–796, 1966.

28. Gajdusek, D. C., N. G. Rogers, M. Basnight, C. J. Gibbs, Jr. and M. Alpers. Transmission experiments with kuru in chimpanzees and the isolation of latent viruses from the explanted tissues of affected animals. *Ann. NY Acad. Sci.* 162: 529–550, 1969.

29. Gardner, R. A., and B. T. Gardner. Teaching sign language to a chimpanzee. *Science* 165: 664–672, 1969.

30. Goodwin, D. Dr. King discusses future role at Yerkes. *Res. Resour. Rep.* 11(10): 11–14, 1978.

31. Gordon, T. P. Reproductive behavior in the rhesus monkey: social and endocrine variables. *Am. Zool.* 21: 185–195, 1981.

32. Gould, K. G., and A. H. Ansari. Chemical alteration of cervical mucus by electrolytes. *Am. J. Obstet. Gynecol.* 145: 92–99, 1983.

33. Goy, R. W., and J. A. Robinson. Prenatal exposure of rhesus monkeys to patent androgens: morphological, behavioral and physiological consequences. In: *Environmental Factors in Human Growth and Development*, edited by V. R. Hunt, M. K. Smith, and D. Worth. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1982, pp. 355–378.

34. Goy, R. W., J. E. Wolf, and S. G. Eisele. Experimental female hermaphroiditism in rhesus monkeys: anatomical and psychological characteristics. In: *Handbook of Sexology*, edited by J. Money and H. Musaph. New York: Elsevier/North-Holland, 1977, pp. 139–156.

35. Graham, C. E. Great apes as models in reproductive biology. In: *Reproductive Biology of the Great Apes*, edited by C. E. Graham. New York: Academic, 1981, pp. 407–427.

36. Gregor, Z. and S. J. Ryan. Complete and core vitrectomies in the treatment of experimental posterior penetrating eye injury in the rhesus monkey. *Arch. Ophthalmol.* 101: 441–450, 1983.

37. Halperin, E. C., G. S. Hass, D. E. Dosoretz, M. Gitterman, A. B. Cosimi, R. M. Linggood, and H. D. Suit. A study of the immunologic effects of lymphoid irradiation in human and nonhuman primates: cellular changes and the potential for transplantation. *Int. J. Radiat. Oncol. Biophys.* 8: 63, 1982.

38. Harrison, M. R., J. Anderson, M. A. Rosen, N. A. Ross, and A. G. Hendrickx. Fetal surgery in the primate. *J. Pediatr. Surg.* 17: 115–122, 1982.

39. Hearn, J. P. Laboratory primates for the development of new methods of fertility control. *Symposium on Recent Advances in Fertility Regulation.* Geneva: WHO, 1981, pp. 164–176.

40. Hearn, J. P. Immunological suppression of fertility in primates. In: *Recent Advances in Primatology*, edited by D. J. Chivers and E. H. R. Ford. New York: Academic, 1978, vol. 4, pp. 141–143.

41. Heberling, R. L., and S. S. Kalter. Endogenous RNA oncornaviruses of nonhuman primates. In: *Recent Advances in Primatology*, edited by D. J. Chivers and E. H. R. Ford. New York: Academic, 1978, vol. 4, pp. 87–97.

42. Held, J. R. Nonhuman primates: their use in biomedical research. In: *Viral and Immunological Diseases in Nonhuman Primates*, edited by S. S. Kalter. New York: Liss, 1983, pp. 3–16.

43. Hendrickx, A., L. R. Axelrod, and L. C. Claborn. Thalidomide syndrome in baboons. *Nature London* 210: 958–959, 1966.

44. Herbert, W. Remembrance of things partly. *Sci. News* 124: 378–381, 1983.

45. Hodgen, G. D. Antenatal diagnosis and treatment of fetal skeletal malformations. *J. Am. Med. Assoc.* 246: 1079–1083, 1981.

46. Hodgen, G. D. Primate models for pregnancy hormone secretion in man: fetal, maternal and placental factors. In: *Animal Models for Research on Contraception and Fertility*, edited by N. J. Alexander. New York: Harper & Row, 1979, pp. 425–436.

47. Horstmann, D. M. The use of primates in experimental viral infections—rubella and rubella syndrome. *Ann. NY Acad. Sci.* 162: 594–597, 1969.

48. Howard, A. N., R. Zschocke, R. Loser, and G. Hofrichter. The use of baboons in lipid pharmacology. In: *The Use of Nonhuman Primates in Cardiovascular Diseases*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980, pp. 361–363.

49. Hunt, R. D. Herpesvirus oncogenesis in New World monkeys. History of herpesvirus oncogenesis and overview of herpesvirus saimiri. In: *Recent Advances in Primatology*, edited by D. J. Chivers and E. H. R. Ford, New York: Academic, 1978, vol. 4, pp. 117–124.

50. Jesse, M. J. Human diseases needing models. In: *The Use of Nonhuman Primates in Cardiovascular Diseases*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980, pp. 377–386.

51. Jewett, D. A. Movement disorders. In: *Nonhuman Primate Models for Human Disease*, edited by W. R. Dukelow. Boca Raton, FL: CRC Press, 1983, pp. 37–44.

52. Johnson, R. Primate model found for respiratory distress syndrome. *Res. Resour. Rep.* 4(3): 1–4, 1980.

53. Johnson, R. Oregon team explores primate fertility. *Res. Resour. Rep.* 4(6): 1–8, 1980.

54. Jonker, M., B. Malissen, and C. Mawas. The effect of in vivo application of monoclonal antibodies specific for human cytotoxic T cells in rhesus monkeys. *Transplantation* 35: 374–378, 1983.

55. *J. Med. Primatol.* Animal experiments benefit animals and man. 11: 389–390, 1982.

56. Kalter, S. S. Primates in viral research. *Ann. NY Acad. Sci.* 162: 511, 1969.

57. Kaplan, J. R. Biomedical implications of behavioral variability in Old World monkeys. In: *The Use of Nonhuman Primates in Cardiovascular Disease*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980. pp. 364–367.

58. Kitt, C. A., D. L. Price, R. Struble, L. Cork, B. H. Wainer, M. W. Becherit, and W. Mobley. Evidence for cholinergic neurites in senile plaques. *Science* 226: 1443–1445, 1984.

59. Kolata, G. Fetal surgery for neural defects? *Science* 221: 441, 1983.

60. Konner, M. Love. In: *The Tangled Wing. Biological Constraints on the Human Spirit.* New York: Harper & Row, 1982, pp. 291–324.

61. Konner, M. Grief. In: *The Tangled Wing. Biological Constraints on the Human Spirit.* New York: Harper & Row, 1982, pp. 325–356.

62. Korman, K. S., J. Ellis, and F. Manti. Effects of an immunoregulating agent on the periodontitis microflora in monkeys. *Abstr. Annu. Meet. Am. Soc. Microbiol.* 83: 42, 1983.

63. Kramsch, D. M., A. J. Aspen, B. M. Abramsunitz, Z. Kreinerdahl, and W. B. Hood. Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys on an atherogenic diet. *N. Engl. J. Med.* 305: 1483–1489, 1981.

64. Kumar, T. C. A., G. F. X. David, and V. Puri. Nasal sprays for controlling ovulation in rhesus monkeys. In: *Recent Advances in Primatology*, edited by D. J. Chivers and E. H. R. Ford. New York: Academic, 1978, vol. 4, pp. 171–175.

65. Landsteiner, K., and E. Popper. Ubertragung der Poliomyelitis acuta auf affen. *A. Immunitaetsforsch.* 2: 377–390, 1909.

66. Lehner, T., S. J. Challacombe, and J. Caldwell. Immunization with *Streptococcus mutans* against dental caries in rhesus monkeys. In: *New Trends and Development in Vaccines*, edited by A. Voller and J. H. Friedman. Baltimore, MD: University Park, 1978, pp. 275–298.

67. Levy, L., S. K. Noordeen, and H. Sansarrieg. Increase in prevalence of leprosy caused by dapsone resistance *Mycobacterium leprae. Morbid. Mortal. Wk. Rep.* 30: 1, 1982.

68. Lewin, R. Brain enzyme is the target of drug toxin. *Science* 225: 1460–1462, 1984.

69. Makulowich, G. S. Primate center investigates health effects of photochemical smog. *Res. Resour. Rep.* 6(8): 1–5, 1982.

70. Malinow, M. R. Regression of atherosclerosis in nonhuman primates. In: *The Use of Nonhuman Primates in Cardiovascular Diseases*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980, pp. 181–220.

71. Malinow, M. R., P. McLaughlin, H. K. Naito, L. A. Lewis, and W. P. McNulty. Effect of alfalfa meal on shrinkage (regression) of atherosclerotic plaques during cholesterol feeding in monkeys. *Atherosclerosis* 30: 27, 1978b.

72. Manser, J. F. Animal models for AIDS. *Res. Resour. Rep.* 7(6): 1–4, 1983.

73. Marx, P., D. Maul, K. Osborn, N. Lerche, P. Moody, L. Lowenstine, R. Hendrickson, L. Arthur, R. Gilden, M. Graveit, W. London, J. Sever, J. Levy, and R. Munn. Simian AIDS: isolation of a type D retrovirus and transmission of the disease. *Science* 223: 1083–1086, 1984.

74. Maugh, T. H., II. FDA approves hepatitis B vaccine. *Science* 214: 1113, 1981.

75. McClure, H. M. Nonhuman primate models for human disease. *Adv. Vet. Sci. Comp. Med.* 28: 267–304, 1984.

76. McClure, H. M., B. Swenson, F. King, J. C. Chermann, F. B. Sinousi, J. Eichberg, C. Saxinger, R. Gallo, H. Alter, H. Masur, and A. Macher. Experimental infection of chimpanzees with lymphadenopathy associated virus. *Morbid. Mortal. Wk. Rep.* 33: 442–443, 1984.

77. McKinney, W. T., E. C. Moran, and G. W. Kraemer. Biological markers of separation induced depression in primate models. In: *Biological Markers in Psychiatry and Neurology*, edited by E. Vsdin and I. Hanin. New York: Pergamon, 1982, pp. 13–22.

78. Michael, R. P., and D. Zumpe. Rhythmic changes in the copulatory frequency of rhesus monkeys (macaca mulatta) in relation to the menstrual cycle and a comparison with the human cycle. *J. Reprod. Fertil.* 21: 199–201, 1970.

79. Miller, D. S., R. R. Reio, N. S. Cetel, R. W. Rebar, and S. C. Yen. Pulsatile administration of low dose gonadotropin releasing hormone: ovulation and pregnancy in women with hypothalamic amenorrhea. *J. Am. Med. Assoc.* 250: 2937–2941, 1983.

80. Miller, J. A. Anxiety and its opposite. *Sci. News* 122: 332, 1982.

81. *Morbid. Mortal. Wk. Rep.* Yellow fever vaccine. 32: 679, 1984.

82. Morse, G. Cancer vaccine trials in monkeys holds promise. *Sci. News* 125: 224, 1984.

83. Mott, G. E., C. A. McMahan, J. L. Kelly, C. Mersinger-Farley, and H. McGill, Jr. Influence of infant and juvenile diets on serum cholesterol, lipoprotein cholesterol, and lipoprotein concentration in juvenile baboons. *Atherosclerosis* 45: 191–201, 1983.

84. Ninan, P. T., T. M. Insel, R. M. Cohen, J. M. Cook, P. Skolnich, and S. M. Daul. Benzodiazepine receptor-mediated experimental "anxiety" in primates. *Science* 218: 1332–1334, 1982.

85. Novy, M. J., and W. W. Walsh. Regulation of estrogen biosynthesis during pregnancy in the rhesus monkey in fetal endocrinology. In: *Oregon Primate Research Center Symposium on Primate Reproductive Biology.* New York: Academic, 1981, p. 65.

86. *Ob/Gyn Topics.* Cervical mucus alterations result in enhanced fertility. 1(5): 1 and 7, 1983.

87. Oh, J. H., H. M. McClure, and E. P. Tuttle. Immune tolerance induced by platelet transfusion in rhesus monkeys. *Kidney Int.* 23: 294, 1983.

88. Ordy, J. M. Neurobiology and aging in nonhuman primates. Advances in behavioral biology. In: *Neurobiology of Aging*, edited by J. M. Ordy. New York: Plenum, 1975, vol. 16, pp. 575–594.

89. Patterson, F. The gestures of a gorilla: sign language acquisition in another pongid species. *Brain Lang.* 5: 72–97, 1978.

90. Pattishall, E. G., Jr. Animal behavior: relation to illness and disease. In: *The Future of Animals, Cells, Models and Systems in Research Development, Education and Testing.* Washington, DC: Nat. Acad. Sci., 1977, pp. 115–123.

91. Petricciani, J. C., H. E. Hopps, B. L. Elisberg, and E. M. Earley. Application of in vitro systems to public health. In: *The Future of Animals, Cells, Models and Systems in Research Development, Education and Testing.* Washington, DC: Nat. Acad. Sci., 1977, pp. 240–251.

92. Prasad, M. R. N. Nonhuman primates as models for evaluation of fertility regulating agents—antiandrogens. In: *Nonhuman Primate Models as Study of Human Reproduction*, edited by T. C. Anand Kumar. Basel: Karger, 1980, pp. 214–218.

93. Premack, D. On the assessment of language competence in the chimpanzee. In: *Behavior of Nonhuman Primates*, edited by A. M. Schier and F. Shollnitz. New York: Academic, 1971, vol 4., pp. 185–228.

94. *Primate News.* Malaria. Oregon Primate Research Center. 21(1): 5, 1984.

95. *Primate News.* Male and female behavioral patterns. Oregon Primate Research Center. 21(1): 17, 1984.

96. *Primate News.* Slow viruses. Oregon Primate Research Center. 21(1): 15, 1984.

97. *Primate News.* Infertility. Oregon Primate Research Center. 21(1): 10, 1984.

98. *Primate News.* Polychlorinated biphenyls and dioxin. Oregon Primate Research Center. 21(1): 18, 1984.

99. *Primate News.* Dietary fats and heart disease. Oregon Primate Research Center. 21(2): 9, 1984.

100. *Primate News.* Microwave radiation. Oregon Primate Research Center. 21(1): 18, 1984.

101. *Primate News.* Hyaline membrane disease. Oregon Primate Research Center. 21(1): 12, 1984.

102. *Primate News.* In vitro fertilization. Oregon Primate Research Center. 21(1): 10, 1984.

103. *Primate News.* New alternatives to in vitro fertilization. Surrogate embryo transfer. Oregon Primate Research Center. 21(1): 11, 1984.

104. *Primate News.* Eye damage from ultraviolet radiation. Oregon Primate Research Center. 21(1): 15, 1984.

105. *Primate News.* Menopausal problems. Oregon Primate Research Center. 21(1): 17, 1984.

106. Provost, P., P. Conti, P. A. Giesa, F. S. Banker, E. Buynak, W. J. McAleer, and M. Hilleman. Studies in chimpanzees of live, attenuated hepatitis B vaccine candidates. *Proc. Soc. Exp. Biol. Med.* 172: 357–363, 1983.

107. Rabin, H. Studies on nonhuman primates with exogenous type C and type D oncornaviruses. In: *Recent Advances in Primatology*, edited by D. J. Chivers and E. H. R. Ford. New York: Academic, 1978, vol. 4, pp. 101–115.

108. Reite, M., and D. S. Snyder. Physiology of maternal separation in a bonnett macaque infant. *Am. J. Primatol.* 2: 115–120, 1982.

109. *Res. Resour. Rep.* Corneal matrix lenses improve vision for cataract patients. 5(6): 1–5, 1981.

110. *Res. Resour. Rep.* Preventing premature labor. 6(8): 7–9, 1982.

111. *Res. Resour. Rep.* Diet on the drug cholestyramine can dramatically shrink arterial plaque in cynomolgus monkeys according to scientists at the Oregon Primate Research Center. 8(10): 12–13, 1984.

112. *Res. Resour. Rep.* Dietary effects on aging studied in monkey colony. 7(6): 5–7, 1983.

113. Romski, M. A., R. A. White, C. E. Millen, and D. M. Rumbaugh. Effects of computer keyboard teaching on the symbolic communication of severely retarded persons: five case studies. *Psychol. Rec.* 34: 39–54, 1984.

114. Ross, R. Recent progress in understanding atherosclerosis. *J. Am. Geriatr. Soc.* 31: 231–235, 1983.

115. Rumbaugh, D. M., T. V. Gill, and E. C. Glaserfeld. Reading and sentence completion by a chimpanzee. *Science* 182: 731–733, 1973.
116. Rumbaugh, D. M., E. S. Savage-Rumbaugh, J. L. Scanlon. The relationship between language in apes and human beings. In: *Primate Behavior*, edited by J. L. Fobes. New York: Academic, 1982, pp. 361–385.
117. Satinoff, E., and P. Teitelbaum. *Handbook of Behavioral Neurobiology. Motivation*, edited by F. A. King. New York: Plenum, 1983, vol. 6.
118. Savage-Rumbaugh, E. S., D. M. Rumbaugh, S. T. Smith, and J. Lawson. Reference: the linguistic essential. *Science* 210: 922–925, 1980.
119. *Sci. News*. Monkey clue to heart disease. 124: 160, 1983.
120. *Sci. News*. Are you my mother? 125(17): 269, 1984.
121. *Sci. News*. First chimps infected with AIDS virus. 126: 121, 1984.
122. *Sci. News*. An anchor to sink one's teeth into. 123(12): 185, 1983.
123. Seabrook, C. Atherosclerosis may be retarded by reducing cholesterol. *The Atlanta Journal*, Atlanta, GA, 1982, March, sect. B: 6.
124. Seyfarth, R. M., and D. L. Cheney. How monkeys see the world: a review of recent research on East African vervet monkeys. In: *Primate Communication*, edited by C. T. Snowden. New York: Cambridge Univ. Press, 1982, pp. 239–257.
125. Shandilya, L., T. B. Clarkson, M. R. Adams, and J. C. Lewis. Effects of gossypol on reproductive and endocrine functions of male cynomolgus monkeys (*Macaca fascicularis*). *Biol. Reprod.* 27: 241–252, 1982.
126. Siegler, H. F., R. S. Metzgar, T. Mohoakumar, and G. M. Stuhlmiller. Human melanoma and leukemia associated antigens defined by primate antisera. *Federation Proc.* 34: 1642–1646.
127. Smith, E. O., and L. D. Byrd. *D*-amphetamine induced changes in social interaction patterns. *Pharmacol. Biochem. Behav.* 22: 135–139, 1985.
128. Sperry, R. Some effects of disconnecting the cerebral hemispheres. *Science* 217: 1223–1226, 1982.
129. Spraque, E. A., R. G. Troxler, D. F. Peterson, R. E. Schmidt, and J. T. Young. Effect of cortisol on the development of atherosclerosis in cynomolgus monkeys. In: *The Use of Nonhuman Primates in Cardiovascular Diseases*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980, pp. 261–264.
130. Stevens, V. C. The use of female baboons for evaluation of immunological methods of fertility control: In: *Recent Advances in Primatology*, edited by D. J. Chivers and E. H. R. Ford. New York: Academic, 1978, vol. 4, pp. 145–151.
131. Stout, C., and M. E. Groover, Jr. Spontaneous versus experimental atherosclerosis. *Ann. NY Acad. Sci.* 162: 89–98, 1969.
132. Strayer, F. F., and J. Strayer. An ethiological analysis of social agonism and dominance relations among preschool children. *Child Dev.* 47: 980–989, 1976.
133. Suomi, S. J. Genetic, maternal and environmental influences on social development in rhesus monkeys. In: *Primate Behavior and Sociobiology*, edited by B. Chiarelli and R. Coruccini. New York: Springer-Verlag, 1981, pp. 81–87.
134. Suomi, S. J., G. W. Kraemer, C. M. Baysinger, and R. D. DeLizio. Inherited and experiential factors associated with individual differences in anxious behavior displayed by rhesus monkeys. In: *Anxiety: New Research and Changing Concepts*, edited by D. F. Klein and J. G. Rabkin. New York: Raven, 1981, pp. 179–200.
135. Suomi, S. J., and H. F. Harlow. Early experience and social development in rhesus monkeys. In: *Social and Personality Development*, edited by M. Lamb. New York: Holt, Rinehart, & Winston, 1978.
136. Taulbee, P. Solving the mystery of anxiety. *Sci. News* 124: 45–46, 1983.
137. Taylor, C. B., G. E. Cox, P. Manalo-Estrella, and J. Southworth. Atherosclerosis in rhesus monkeys. II. Arterial lesions associated with hypercholesterolemia induced by dietary fat and cholesterol. *Arch. Pathol.* 74: 16–34, 1962.
138. Taylor, C. B., P. Manalo-Estrella, and G. E. Cox. Atherosclerosis in rhesus monkeys. V. Marked diet-induced hypercholestolemia with xanthomatosis and severe atherosclerosis. *Arch. Pathol.* 76: 239–249, 1963.
139. Taylor, C. B., D. E. Patton, and G. E. Cox. Atherosclerosis in rhesus monkeys. VI. Fatal myocardial infarction in a monkey fed fat and cholesterol. *Arch. Pathol.* 76: 404–412, 1963.
140. Tigges, J., M. Tigges, N. A. Cross, R. L. McBride, W. D. Letbetter, and S. Anschel. Subcortical structures projecting to visual cortical areas in squirrel monkeys. *J. Comp. Neurol.* 209: 29–40, 1982.
141. Tuchmann-Duplessis, H. Teratogenic drug screening: present procedures and requirements. *Teratology* 5: 271–286, 1972.
142. Vesselinovitch, D. The study of atherosclerosis with animal models. *Comp. Pathol. Bull.* 13: 1–4, 1981.
143. Wallen, K. Influence of female hormonal state on rhesus sexual behavior varies with space for social interaction. *Science* 217: 375–376, 1982.
143a. Wallen, K., M. Davis-DaSilva, D. R. Mann, S. Gaventa, and J. C. Lovejoy. Suppression of ovulation and sexual behavior in group-living rhesus by GNRh treatment. *Biol. Reprod.* 30, *Suppl.* 1: 76, 1984.
144. Wallen, K., L. A. Winston, S. Gaventa, M. Davis-DaSilva, and D. C. Collins. Periovulatory changes in female sexual behavior and patterns of ovarian steroid secretion in group-living rhesus monkeys. *Horm. Behav.* 18: 431–450, 1984.
144. Wallen, K., L. A. Winston, S. Gaventa, M. Davis-DaSilva, and D. C. Collins. Periovulatory changes in female sexual behavior and patterns of ovarian steroid secretion in group living rhesus monkeys. *Horm. Behav.* 18: 431–450, 1984.
145. Whitehouse, P. J., D. L. Price, R.G. Strubk, A. W. Clark, and J. T. Coyle. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 215: 1237–1239, 1982.
146. Wiesel, T. N. Postnatal development of the visual cortex and the influence of environment. *Nature London* 299: 583–591, 1982.
147. Wilson, M. E., T. P. Gordon, and D. C. Collins. Variation in ovarian steroids associated with the annual mating period in female rhesus (*Macaca mulatta*). *Biol. Reprod.* 27: 530–539, 1982.
148. *Wisconsin Regional Primate Research Center, University of Wisconsin-Madison Annual Progress Report.* Jan. 1–Dec. 31, 1983, p. 20.
149. Wissler, R. W. Perspectives on cardiovascular research in primates. In: *The Use of Nonhuman Primates in Cardiovascular Diseases*, edited by S. S. Kalter. Austin, TX: Univ. of Texas Press, 1980, pp. 15–32.
150. Wissler, R. W., H. Brooks, D. Vesselinovitch, F. Paskkow, R. P. Holland, and R. Hughes. Studies of acute myocardial infarction in atherosclerotic rhesus monkeys. *J. Med. Primatol.* 4: 362–363, 1975.
151. Wissler, R. W., P. Vesselinovitch, R. Hughes, D. Turner, and L. Frazier. Arterial lesions and blood lipids in rhesus monkeys fed human diets. *Exp. Mol. Pathol.* 38: 1, 1983.
152. Woods, S. C., E. C. Lotter, D. McKay, and D. Porte, Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature London* 282: 503–505, 1979.
153. *World Health Organization Chronicle.* WHO position on the need for nonhuman primates in biomedical research. 31: 43, 1982.
154. Yarbrough, C. Adolescent aggressive behavior studied by Dr. I. Bernstein. *Inside Yerkes Newsletter* 4(1): 3–4, 1984.
155. Yerkes, R. M. *Almost Human*. New York: Century, 1925, p. 180.
156. Young, M. D. Monkeys and malaria. In: *Nonhuman Primates and Medical Research*, edited by G. H. Bourne. New York: Academic, 1973, pp. 17–23.
157. Young, W., R. W. Goy, and C. H. Phoenix. The hormones and sexual behavior. Broad relationships exist between the gonadal hormones and behavior. *Science* 143: 212–218, 1964.
158. Zebenek, G., and S. J. Ryan. Complete and core vitrectomy in the treatment of experimental posterior penetrating eye injury in the rhesus monkey. *Arch. Ophthalmol.* 101: 441–450, 1983.

The APS Photograph Collection

Over the years the American Physiological Society has accumulated a large collection of photographs. Until a few years ago, these were almost unusable, scattered here and there in envelopes, files, and boxes around the APS Headquarters. Recently they have been organized by Grace Gurtowski and Toby Appel and are now available as a resource for physiologists and historians. This article surveys the strengths and limitations of the collection and suggests what other photographs might be desirable to add to it.

By far the largest portion of photographs in the collection consists of portraits, both formal and informal, of past and present members of APS. Among the oldest portrait photographs are those of all twenty-eight men who were designated charter members of APS at the Organizational Meeting of the Society on December 30, 1887. These images, some of rather obscure individuals, were collected nearly fifty years ago for use in the semicentennial history of APS. Photographs have also been regularly collected of all fifty-seven presidents of APS from Henry P. Bowditch to John B. West. These have been published in the official APS histories and also used to create the five composite pictures of APS presidents that adorn the walls of the APS Conference Room.

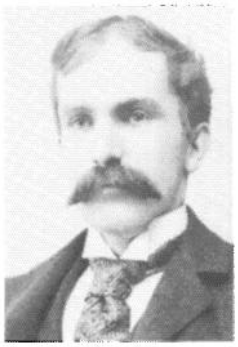
From various sources, APS has acquired many photographs of other members, as well as some nonmembers. Perhaps the chief source of these has been *The Physiologist*. Whenever, in recent years, an author of a biographical notice, obituary, departmental history, or historical article has submitted a photograph of historical interest, it has been saved and catalogued by individual and subject into the collection. Another major source has been donations from members of APS. In the past year, several significant donations have been made. Among them are photographs collected by E. S. Nasset and J. R. Murlin, including several of early biochemist members of APS, donated by Mrs. E. S. Nasset; a collection of international leaders in reproductive physiology, donated by M. C. Shelesnyak; photographs taken by Fred A. Hitchcock in the 1940s and 1950s, donated by Jay B. Dean; and a series of photographs of Maurice B. Visscher, donated by Irwin Fox. Despite the wealth of photographs now in the collection, coverage of APS membership has been uneven. Only a few photographs have been collected of the most distinguished class of members of the Society, the Honorary Members. And, until recently, APS had received few photographs of women and no photographs at all of black physiologists. A. Clifford Barger, Co-Chairman since 1968 of the Porter Development Committee, has this past year contributed a number of photographs of black members in APS, and Horace Davenport has donated several snapshots taken in the 1950s of women physiologists. Toby Appel has been actively collecting photographs of early women members of APS for use in an exhibit at the Spring meeting next year.

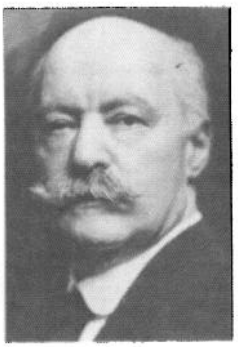
A second important series of photographs in the APS Photograph Collection consists of photographs taken at APS Spring and Fall meetings and at International Congresses. The oldest and most valuable photographs in this group are three panoramic photographs, each over three feet long, taken as a souvenir of all those who attended a given meeting. The earliest of these is of the second meeting of the Federation, held in 1914 at the Washington University School of Medicine, St. Louis. The other two panoramas are of the Federation meeting in St. Louis in 1923 and of the XIIIth International Physiological Congress held at Harvard Medical School, Boston, in 1929. There are only a handful of other photographs taken at APS meetings before 1950. But from 1950 through 1961, APS had the good fortune to have had an unofficial meetings photographer in the person of Horace Davenport. In this period, he took well over a hundred snapshots of physiologists strolling the Atlantic City Boardwalk at Spring meetings and enjoying the fresh air on the campuses of colleges and universities at Fall meetings. For several years, he took informal photographs of the APS Council, of which he was a member. The negatives of this remarkable collection were given to APS for use in Wallace Fenn's 75-year history of the Society. A number of the photographs were published in that volume, but the rest of the negatives were left unprinted until a few months ago. With the help of Dr. Davenport, the subjects of the photographs have now been identified and the collection is available for use.

After 1961, the documentation of APS meetings becomes slender indeed. The one exception is the 1963 Fall meeting, which marked the 75th anniversary of APS. An amusing set of photographs was taken of past presidents wearing halos of wire and aluminum foil presented to them for the occasion. In the later 1960s and in the 1970s, no official or unofficial photographer was on hand to record meetings. Only on rare occasions were pictures taken of presentations of awards, of exhibits, or of poster sessions. There are almost no pictures for any period in APS history of APS committees, APS special interest groups, or APS sections and their activities. It is one of the purposes of this article to remedy this state

APS Volunteer Photographer Wanted

A member is wanted with a good camera and flash attachment to take one or two rolls of black and white photographs at upcoming APS Spring and Fall meetings. Among the photographs desired are those of Council, of awards presented at the Business Meeting, and of special speakers and events. Film and processing will be supplied by APS. If you would like to volunteer, please write to Toby Appel, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814 (301/530-7105).





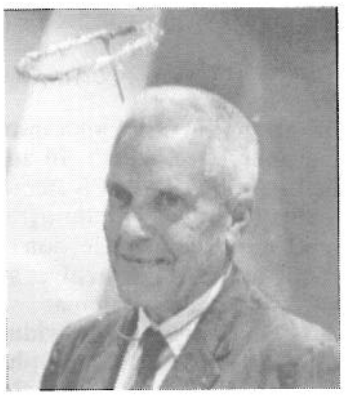
Left to right:

Charter Member: Frederick W. Ellis, a student of Bowditch, who practiced opthamology and maintained a private laboratory

Past President: Samuel J. Meltzer, Rockefeller Institute, president of APS, 1911-1913

Blacks in Physiology: Joseph L. Johnson, Howard University, the first black member of APS, elected in 1934 (donated by A. C. Barger)

Women in Physiology: Charlotte Haywood, Mount Holyoke College, in laboratory at Woods Hole, c. 1927 (courtesy of MBL Library Archives)



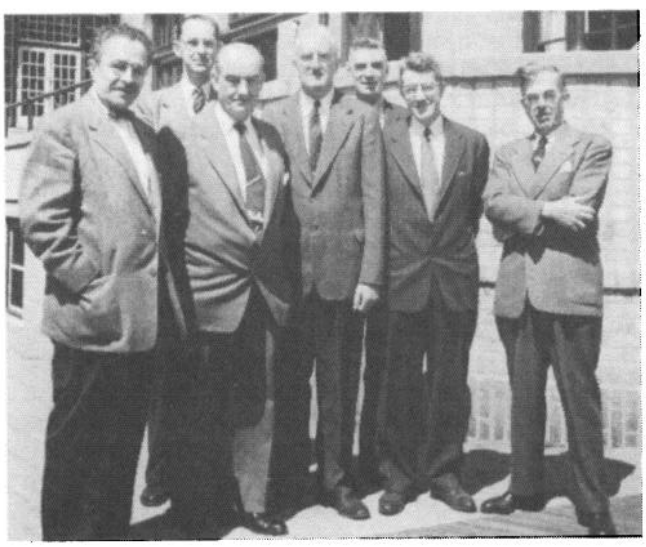
Left to right:

Spring meetings: Martin Larrabee, Johns Hopkins University, in Atlantic City, Spring 1954 (photo by H. W. Davenport)

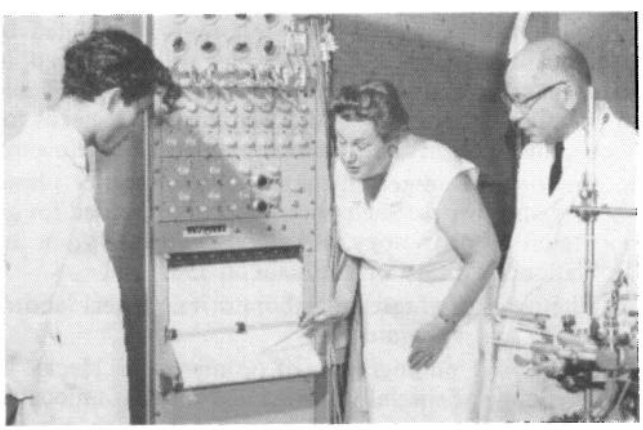
Fall meetings: Freeman H. Quimby, NASA, at the University of Utah, Fall 1951 (photo by H. W. Davenport)

75th Anniversary Celebration: Bruce Dill, Coral Gables, Florida, Fall 1963

Physiologists at Work: Michael B. Maron, Steven Horvath, James Wilkerson and Jeffrey Gliner at the Santa Barbara Marathon, 1975 (donated by M. B. Maron)



APS Council: Council in Atlantic City, Spring 1954 (photo by H. W. Davenport)



Physiologists at Work: T. Kobayashi, Williamina Himwich and Harold Himwich, Thudichum Psychiatric Research Institute, Galesburg, Illinois, c. 1962 (donated by W. A. Himwich)

Walter B. Cannon and the Department of Physiology, Harvard Medical School, 1936 (donated by H. K. Wills)

of affairs by the appointment of a meetings photographer (see below). In addition to APS Spring and Fall meetings, the APS Photograph Collection contains a small number of photographs taken at international meetings. A large collection of such photographs can be found in the IUPS Archives at the American Philosophical Society, Philadelphia.

These two series – individuals and meetings – account for nearly all the photographs in the collection. In other categories, some of considerable importance to historians of physiology, the collection is decidely weak. There are at present only a small number of photographs of physiologists at work in laboratories and in the field; of departments of physiology (however, there are several photographs of W. B. Cannon's department at Harvard); of buildings; of student laboratories; and of apparatus. Of those that we do have, most were submitted with departmental histories and other historical articles for *The Physiologist* and have been published. Finally, the collection includes occasional photographs of the Beaumont campus and the APS staff.

Pictures Wanted

All donations to the APS photograph collection are greatly appreciated. We would like to make APS the chief repository in the country for photographs related to American physiology. Photographs will be stored in folders and catalogued, and copies will be made available to members and others at cost. Among special needs for Centennial exhibits and publications are the following.

1. Photographs, especially early photographs, of physiologists at work. Such photographs are needed for an exhibit on physiology in America to be shown at the National Library of Medicine in 1987.
2. Photographs of research laboratories, student laboratories, and apparatus.
3. Additional photographs of women and blacks in physiology. Especially needed and thus far unlocated is a good photograph of Caroline tum Suden, a benefactor of the Society and for whom of the Caroline tum Suden Professional Opportunity Awards were named. Also wanted are photographs taken at the 1967 Fall meeting held at Howard University. Lists of early women and black members of APS are available on request.
4. Photographs of Honorary Members. A list is available on request.
5. Photographs of APS committees, task forces, special interest groups and sections, and their activities.
6. Informal photographs taken at APS meetings, especially at meetings before 1950 and at recent meetings.

Toby Appel
Historian/Archivist

Stephen Hales Memorial

Stephen Hales (1677–1761) was an eminent English physiologist who made important contributions to cardiovascular and respiratory physiology. For example, he is credited with the first measurement of arterial blood pressure. He spent most of his working life as Vicar of St. Mary's Church, Teddington near London, where he died and was buried in a tomb under the church tower. The church subsequently fell out of use; the gravestone became badly decayed and its inscription illegible. Recently, however, the church has once more become the center of an active parish and is being restored as limited funds allow.

On the initiative of Professor E. T. Pengelly of the University of California, Davis, an appeal was launched to save the gravestone from further decay and to restore the inscription. Dr. Pengelly is a plant physiologist and Hales is well known to that group through his contributions, particularly on the ascent of sap. The APS was made aware of the appeal and Council decided to donate $250, which was matched with an equal sum from an APS member. Work on restoring the gravestone and surroundings is now underway. If you are in London, the church is well worth a visit for its historical connections with Stephen Hales.

Careers for Physiologists in Departments of Biological and Animal Sciences

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A recent survey by the American Physiological Society (1) identified 215 programs in the United States and its territories that offer specialized training in physiology. Of the total, 198 or 92.1% grant doctoral degrees. Slightly more than half of these doctoral programs (110, 55.6%) were clearly associated with medical schools. The remaining 88 programs (44.4% of total) are the topic of this report.

The majority (70 programs, 79.5%) of nonmedical physiology Ph.D. programs were located within departments of biological science. Twelve other universities (13.6%) had a separate department of physiology either alone or in combination with another biomedical science such as anatomy or had interdepartmental programs in physiology. Examples are the University of Illinois at Urbana-Champaign and the University of California at Berkeley. Half of these latter 12 programs were located at universities that had veterinary schools which did not have a separate physiology department. North Carolina State and the University of Wyoming are typical of these programs. Six other physiology departments (6.9%) were located within schools of veterinary medicine. Iowa State is an example.

There were a few other universities that had allopathic and/or osteopathic medical schools, veterinary schools, and animal physiology programs all on the same campus. The physiology faculty in these schools were integrated into a single program or department and participated in the medical school program to varying degrees. Examples are the University of California at Davis and Michigan State University. These schools were contacted directly for numbers of faculty and doctoral students not primarily affiliated with the medical school. Other schools had medical and nonmedical faculty as part of a single interdisciplinary program, but in practice medical and nonmedical components of the programs were almost entirely separate. Usually in these cases the medical school was located some distance away from the main campus. The Pennsylvania State University and Rutgers University are in this category. Finally, some schools had distinct medical and nonmedical physiology programs that had entirely separate faculty. Examples are the University of Arizona, University of California at San Diego, University of Kansas, University of Minnesota, Iowa State University, Ohio State University, Oklahoma State University, and the State University of New York at Buffalo.

Estimation of the size of these programs, including both faculty and students, has posed substantial difficulty. Statistics from the National Research Council indicate that a Total of 1,570 research doctorates were granted during the 5-year period between July 1976 and June 1981. A recent survey of research doctoral programs in physiology (2) described and evaluated 101 programs that had awarded at least 11 Ph.D. degrees during FY 1976-78. These programs accounted for 87% (1,369) of the doctoral degrees awarded during FY 1976-81. Table 1 has been compiled from that evaluation (2), and it summarizes the estimated size of these larger doctoral programs. Briefly, nonmedical school physiology programs employed ~28% (556 positions) of the total faculty, awarded 36% of the 1,369 doctoral degrees accounted for by this survey, and enrolled (as of June 1980) ~39% (632 students) of the full-time graduate physiology students. Approximately 39 medical schools and 36 nonmedical programs were not tabulated in this survey; presumably the remaining 13% of degrees (210) were largely awarded by these programs.

Although informative, the data in Table 1 were subject to some question because a perusal of 30 program descriptions (3) about research activities of faculty in nonmedical programs suggested that on the average only 20-30% of the faculty were physiologists. Based on this sample it appeared likely that the total employment opportunities for physiologists might have been significantly overestimated. Second, the Jones, Lindzey, and Coggeshall report (2) did not include data for 41% of the small nonmedical programs. To obtain a more accurate estimate of the number of physiologists in programs not associated with medical schools, a questionnaire was sent to each of the 88 programs that were identified by APS (1). Department and program heads were queried about numbers of full and part-time faculty and students who had their primary effort in physiology, as well as the number of doctoral degrees with a specialization in physiology awarded during the past 5 years. Approximately 76% of the schools responded, and the results are summarized in Table 2. Most of the nonresponders were small programs, but a few were of significant size. Data for these were abstracted from Refs. 2 and 3 and included in Table 2. Survey results clearly indicated that the estimates in Table 1 were too low, rather than an overestimation. An additional 199 full-time faculty positions and 295 more full-time students were reported.

In fact, the opportunities for physiologists may still be underestimated in Table 2 because there also appears to be a significant number of programs offering specialty training in physiology that were not included in the APS survey. Specifically, a recent description of graduate programs in zoology tabulated by the Educational Testing Service (4) indicates there are at least 109 programs in zoology of which 81 (74%) are doctoral programs.

Table 1
Summary of 101 Research Doctorate Programs in Physiology[a]

Type of Department	*n*	Total Full-Time Faculty	Total Ph.D. Students	Total Awarded FY 1976-1980	Average Annual Ph.D./Year
Physiology, medical school	71	1,408	984	882	2.5
Physiology, nonmedical (including interdisciplinary programs)	12	229	275	167	2.8
Biological sciences	12	138	217	139	2.3
Physiology, veterinary	6	109	65	122[b]	4.1[b]
Total nonmedical	30	476	557	428	
Grand total	101	1,964	1,616	1,369[c]	

[a]Which awarded 11 or more Ph.D. FY 1976-78. Taken from Reference 2. Smaller programs were excluded by this study. See Table 2 also.
[b]One school accounts for 58% of graduates (Okalhoma State Univ).
[c]National Research Council reported a total of 1570 research doctorates in physiology were awarded between FY 1976-FY 1980. These data, therefore, account for approximately 87% of the total.

Table 2
Survey of 88 Doctoral Programs in Physiology Which Were Not Part of a Medical School Department

	Faculty		Doctoral Students		Ph.D. Awarded FY 1978-83
	Full-Time	Part-Time	Full-Time	Part-Time	
Responded (76%)	562	48	716	35	616
Estimated[a]	193		211		
Total	755	48	927	35	616

[a]Taken from Refs. 2 and 3.

About 62% of the doctoral programs offer a specialization or at least some training in animal physiology. The total number of faculty in these programs was 973, of which less than half (410, 42%) were accounted for in the APS survey. Again, program descriptions (3) were surveyed for 20% of these zoology departments, and on average 18% ± 3% of the total faculty appeared to be physiologists and/or were pursuing research in this discipline. Thus an estimated 100 additional faculty positions may be available through this source. Finally, a preliminary survey of Peterson's Guide (3) indicates that neurobiology programs may be another significant career opportunity for physiologists. A total of 93 neuroscience and neurobiology programs are described, and almost half of these do not appear to be associated with medical schools. A case in point is the neurobiology program at Northwestern (Evanston), which has 62 faculty and enrolls about 75 students. Fully a third of the faculty appear to be physiologists. In summary, nationwide probably almost half of all physiology faculty are not directly connected with a medical school department.

Since many physiologists are located in biological science departments, two other goals of this report were *1)* to compare the physiologists in this setting to their medical school counterparts and *2)* to characterize the types of programs found outside the traditional medical school setting. A general characteristic of a career in a biological science department is thought to be a higher teaching load and relatively less time for research. Data in Table 3 suggest that this may indeed be the case. On the average, nonmedical departments were slightly smaller and the faculty-to-graduate student ratio was ~60% lower than was reported for medical schools. There are no tabulated data available that reflect undergraduate teaching loads. In general, research funding from national sources was also less in nonmedical programs, and the publication rate was half that of the average medical school. There are, however, some notable exceptions found mainly among the larger programs (University of California at Davis, University of Illinois at Urbana-Champaign, University of Minnesota, The Pennsylvania State University, Purdue University, and Rockefeller University for example). These schools were fully comparable to (and in some cases superior to) the

Table 3
Characteristics of Physiology Faculty in Doctoral Programs

Mean Value	Type of Program: Medical (*n* = 71)	Nonmedical (*n* = 30)	Combined (*n* = 101)
No. of faculty	21	16	19
Faculty/student	1.41	0.85	1.22
%Faculty with national funding	56%	42%	52%
Annual publications/faculty	1	0.5	0.9
Faculty reputation[a]	3.1	2.7	3.0

[a]Scale 0-5, low to high (mean 3.0 ± 0.7). Data tabulated from Ref. 2.

average medical school program in funding, publications, and national reputation.

Attempts to characterize the course content of nonmedical programs were made by reading both college catalogs and program descriptions in Peterson's Guide. A tabulation of the areas of specialization within physiology programs provided by APS (1) was also done. Programs were highly individual. In addition to specialization in physiology, zoology, and animal and poultry science, frequent areas of secondary specialization were biochemistry (including nutrition), anatomy and histology, biophysics, and pharmacology. Within the discipline of physiology, over 50% of the programs in biological science departments offered training in the following specialties: cell, endocrine, comparative, neurophysiology, and developmental physiology. In contrast, in medical departments over 80% of the programs offered specialization in neurophysiology, cardiovascular physiology, and endocrine physiology, closely followed by cellular and respiratory physiology. Opportunities for specialization in the physiology of other organ systems were generally much greater in medical schools. These data are spceifically detailed in Table 4.

Finally, Table 5 lists some of the largest programs which have been identified. Rankings have been done both by total full-time faculty and by total number of

Table 4
Areas of Specialization Within Physiology Programs[a]

	Types of Departments			
Specialty	Medical Physiology	Biological Sciences	Veterinary Physiology or Animal Science	Total Nonmedical
Cell	71.8[b]	68.7	87.5	75.0
Cardiovascular	81.8	19.4	43.8	29.5
Comparative	15.6	58.2	43.8	57.9
Endocrine	80.9	68.7	93.8	72.7
Environmental	20.0	50.8	50.8	53.4
Exercise	36.4	17.9	25.0	23.9
Gastrointestinal	34.5	11.9	43.8	18.2
Metabolism	38.2	32.8	43.8	37.5
Muscle	55.4	19.4	50.0	19.3
Neuro	83.7	53.7	81.2	65.9
Nutritional	12.7	22.4	18.8	19.3
Renal	37.3	1.5	18.8	5.7
Reproductive	51.8	41.8	75.0	53.4
Respiratory	68.2	20.9	43.8	26.1
No. of departments	110	68	12	88[c]

[a]Tabulated from Ref. 1.
[b]Percent of total departments of that type which offer the specialty.
[c]Includes data from 8 interdepartmental programs not tabulated separately.

Table 5
Examples of Large Physiology Doctoral Programs Which Are Not Part of a Medical School[a]

No. of Faculty[b]		Total No. of Doctoral Students[c]		Doctorates Awarded FY 1978-1983	
University of California, Davis	63[d]	Univ. of Illinois, Urbana-Champaign	72	Univ. California, Davis	41[e]
Rockefeller University	34	Univ. California, Davis	52	Univ. Illinois at U.C.	37
North Carolina State Univ.	29	Univ. of California, Santa Barbara	50	Univ. of Washington	30
Northwestern University, Evanston	27[d]	Northwestern Univ.	37	Univ. of California, Berkeley	23
Pennsylvania State Univ., University Park	25[d]	U. California, Berkeley	29	Rockefeller Univ.	23
Rutgers University	25[d]	Pennsylvania State Univ., Univ. Park	25	Univ. Pennsylvania (Biology)	22
University of Illinois, Urbana-Champaign	24	Univ. of Minnesota	25	Penn State Univ.	21[e]
Iowa State University	22	Univ. of Washington	25	Univ. Minnesota	21
Colorado State University	22	Rockefeller Univ.	24	Rutgers Univ.	18[e]
University of Minnesota	18	Univ. of Maryland	23	Univ. of Wisconsin, Madison	17
Cornell University	18	Univ. of Texas	22	Univ. of Kansas	17

[a]Tabulated by direct survey of 88 nonmedical programs listed in Ref. 1. Data from nonrespondents estimated from Refs. 2 and 3. Zoology programs with a major in physiology and neurobiology programs are not included unless described in the physiology program listing in Ref. 3 or included in Ref. 1.
[b]Full-time faculty who are exclusively or primarily physiologists.
[c]Does not include M.S. students.
[d]Excludes medical school physiology faculty.
[e]Excludes students supervised by medical school physiology faculty.

full-time doctoral students. These rankings should be regarded as approximations. Information was collected by a direct survey, but only 76% of those surveyed provided the requested information. Furthermore, some large animal physiology programs have not been included (Michigan State, for example) because it was not possible to separate medical and nonmedical components nor were data from zoology departments, neurobiology programs, or cell physiology programs included.

Taken together, the results of this study indicate that substantial career opportunities in physiology exist outside of the "traditional" medical school setting. As many as 850 faculty positions may be available in these programs. Probably a significant number of programs in biological science departments are characterized by heavy teaching loads and relatively less emphasis on research. However, there are notable exceptions, particularly in some of the larger programs. The research productivity of faculty in these latter schools appeared entirely comparable to that of medical school colleagues. Another major difference between medical and nonmedical programs is the relatively greater emphasis by the latter on animal, comparative, and environmental physiology. Biological science departments also generally had few opportunities for specialization in organ system physiology such as renal, respiratory, and cardiovascular. However, both types of programs had extensive offerings in cell and neurophysiology. Thus the recently graduated physiologist has a wide range of academic opportunities available.

References

1. *Institutions Awarding Academic Degrees with a Major in Physiology.* Bethesda, MD: Am. Physiol. Soc., 1983.
2. *An Assessment of Research Doctorate Programs in the United States: Biological Sciences,* edited by L. V. Jones, G. Lindzey, and P. A. Coggeshall. Washington, DC: Natl. Acad. Sci., 1982.
3. *Peterson's Guide to Graduate Programs in the Biological, Agricultural, and Health Sciences 1985.* Princeton, NJ: Peterson's Guides, 1985.
4. *Director of Graduate Programs, 1984-1985. Volume A: Agriculture, Biological Sciences, Psychology, Health Sciences and Home Economics* (9th ed.). Princeton, NJ: Educational Testing Sources, 1983.

Announcements

Richard Bing Award for Young Investigators

The Richard Bing Award competition for young investigators (35 years old or less) will be held at the XII World Congress of the International Society for Heart Research in Melbourne, Australia, 9–13 February 1986. *Deadline for receipt of applications*: 1 September 1985. *Information*: Dr. N. S. Dhalla, Secretary General ISHR, Department of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada R3E 0W3.

Peter Harris Distinguished Scientist Award

The Peter Harris Distinguished Scientist Award, established by the International Society for Heart Research, will be presented at the XII World Congress of ISHR in Melbourne, Australia, 9–13 February 1986. This award is open to any individual with an outstanding record of research (basic or clinical), primarily in the field of the cardiovascular system. *Deadline for nominations* (in the form of a letter describing the name and address of the individual, field of investigation, and reasons for distinction): 1 September 1985. *Address*: Dr. N. S. Dhalla, Secretary General ISHR, Department of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada R3E 0W3.

Volvo Awards for Low Back Pain Research 1986

The Volvo Company of Göteborg, Sweden, will sponsor three prizes of US $6,000.00 each. Awards will be made competitively on the basis of scientific merit in *1*) clinical studies, *2*) bioengineering studies, and *3*) studies in other basic science areas. Papers submitted for the content must contain original material, not previously published or submitted for publication. Multiple authorship is acceptable, and manuscripts should be in the form of a complete report, not exceeding 30 typewritten pages, double-spaced, and suitable for submission to a scientific journal. One of the authors should be prepared, at his own expense, to attend the meeting of the International Society for the Study of the Lumbar Spine, 4–8 June 1986, in Dallas, TX, to present the paper and receive the award. Selection will be made by a board of referees from the fields of clinical medicine, bioengineering, and biochemistry.

Deadline: send five copies of each submitted paper to reach Göteborg not later than 2 January 1986. *Address for correspondence*: Prof. Alf L. Nachemson, Dept. of Orthopaedic Surgery I, Sahlgren Hospital, S-413 45, Göteborg, Sweden.

Meeting of Shock Society

The 8th Annual Meeting of the Shock Society will be held at Hunt Valley (Baltimore), MD, on 9–12 June 1985. *Information*: Shock Society, c/o Sherwood M. Reichard, Medical College of Georgia, Augusta, GA 30912.

Meeting of International Society for Heart Research

The Eighth Annual Meeting of the American Section of the International Society for Heart Research and Satellite Symposium, Heart Metabolism, for the 30th International Congress of Physiological Sciences will be held in Winnipeg, Canada, on 8–11 July 1986. *Information*: Dr. R. E. Beamish, Experimental Cardiology Section, Department of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada R3E 0W3.

Meeting of American Society for Cell Biology

The 25th Annual Meeting of the American Society for Cell Biology will be held in Atlanta, GA, on 18–22 November 1985. *Deadline for receipt of abstracts*: 14 June 1985. *Information*: American Society for Cell Biology, 9650 Rockville Pike, Bethesda, MD 20814. Phone: 301/530-7153.

Gerald S. Kanter Appointed to National Advisory General Medical Sciences Council

APS member Gerald S. Kanter has been appointed to a 4-year term on the National Advisory General Medical Sciences Council. He is associate dean for graduate studies and research and a professor of physiology at Albany Medical College, Albany, NY. The council is composed of leaders in the biological and medical sciences, education, and public affairs. Its members review applications for research and research training grants and make recommendations to the secretary of the Department of Health and Human Services and the directors of the National Institutes of Health and the National Institute of General Medical Sciences (NIGMS) on policy matters and science manpower needs related to the Institute's programs.

Dr. Kanter was born in New York City. He received a B.S. degree in chemistry from Long Island University and a Ph.D. in physiology from the University of Rochester, Rochester, NY. He has been on the faculty of Albany Medical College since 1952. During a leave of absence in 1963 and 1964, Dr. Kanter served as a branch chief at the U.S. Army Institute of Environmental Medicine in Natick, MA. His research is focused on temperature regulation and environmental physiology, body fluid and electrolyte regulation, and kidney function.

John F. Murray Appointed to National Heart, Lung, and Blood Advisory Council

APS member John F. Murray, chief, Chest Service, San Francisco General Hospital, and professor of medicine, University of California, San Francisco, has been appointed to the National Heart, Lung, and Blood Institute's Advisory Council. As a council member, Dr. Murray will take part in the evaluation of the Institute's cardiovascular, blood, and lung diseases programs and will make recommendations to the institute director and NIH director, concerning directions, goals and priorities of these programs.

Born in Mineola, New York, Dr. Murray received an A.B. from Stanford University and his M.D. from Stanford University School of Medicine. He has also received an honorary Doctorate of Science degree from the University of Paris VII. In addition to his present position at San Francisco General and the University of California, San Francisco, Dr. Murray is also on the senior staff, Cardiovascular Research Institute, University of California, and is a member of the Governing Board of the American Board of Internal Medicine.

Future Meetings

1985	
Joint APS/The (British) Physiological Soc Mtg	Sept. 12-14, Cambridge (UK)
APS Fall Meeting	October 13-18 Niagara Falls/SUNY, Buffalo
1986	
FASEB Annual Meeting	April 13-18, St. Louis
IUPS Congress	July 12-20, Vancouver, Canada
APS Fall Meeting	Oct. 5-10, New Orleans
1987	
*FASEB Annual Meeting	March 29-April 3 Washington, DC
APS Fall Meeting	October 11-16, San Diego
*APS Centennial Celebration	

New Handbook on the Respiratory System

The first volume in the new *Handbook of Physiology* on the respiratory system is now available. *Circulation and Nonrespiratory Functions* was edited by Alfred P. Fishman and Aron B. Fisher.

The previous edition of the *Handbook* section on respiration dealt primarily with the function of the lungs from the standpoint of traditional organ physiology. It included such familiar topics as lung volumes and ventilation, mechanical properties of the lungs and thorax, control of breathing, and respiratory gas exchange. This edition not only delves deeper into these aspects of respiratory physiology but also extends into the newer fields of respiratory biology. The broader sweep is exemplified by topics that had no previous counterparts: development and growth of the lungs, pulmonary circulation, pulmonary metabolism and pulmonary defense mechanisms.

The emphasis on quantification, sampling, and reconstruction has added new dimensions to correlations between physiological behavior and anatomical structure. The fruitfulness of this approach is evident in the first two chapters of this volume, which deal with lung development and growth and lung cell biology. The morphological underpinnings of physiology are also evident in the succeeding two chapters, which deal with pulmonary circulation and pulmonary interstitial spaces and lymphatics.

Ultrastructure and biochemistry permeate the next eight chapters, which deal with the metabolism of lung cells and the metabolic functions of the lungs. The first three of these chapters describe oxygen utilization, intermediary metabolism, and protein synthesis by the lung. The subsequent chapters turn to the special metabolic functions of the lungs: surfactant turnover, the handling of biologically active amines and peptides, and the involvement of the lungs in the processing of prostaglandins and lipoproteins. The distinction between substances produced within the lungs that act locally and others that act afar is of great physiological interest in these chapters. Another important concept is that without the intervention of the metabolically active pulmonary capillary endothelium—a huge expanse situated at the gateway to the systemic circulation—vital organs (such

as the brain and heart) would constantly face the threat of noxious, bioactive materials either leaving or bypassing the liver. Finally, these chapters on pulmonary metabolism place the composition of arterial blood in a new light: just as concentrations and partial pressures of the respiratory gases can be used to judge the effectiveness of the lungs in gas exchange, so also arterial levels of biologically active materials can signal the adequacy of their nonrespiratory functions.

The final chapters are concerned with pulmonary defense mechanisms, from secretions and cilia in the conducting airways to macrophages in the respiratory tract. In these chapters, ultrastructure and molecular biology intertwine with the physiological concepts of integration and regulation. The volume closes by dealing with events in the bloodstream: coagulation, fibrinolysis, and interactions between formed elements of the blood and the endothelial lining. In these chapters the broad sweep of structure-function relations enlarges to encompass lessons of cell biology, molecular genetics, and immunology.

The chapters of this volume provide a comprehensive, systematic, and analytic overview of current understanding of the pulmonary circulation, pulmonary interstitial space, and pulmonary water exchange. A list of symbols and abbreviations used in the section is included.

Topics of the remaining volumes in *The Respiratory System* and their editors are the control of breathing, Neil S. Cherniack and John G. Widdicombe; mechanics of breathing, Peter T. Macklem and Jere Mead; and gas exchange, Leon E. Farhi and S. Marsh Tenney. The section editor is Alfred P. Fishman.

Circulation and Nonrespiratory Functions contains 584 pages and 241 figures. The list price is $136.00 but may be ordered by APS members for $109.00. Please order directly from the American Physiology Society, 9650 Rockville Pike, Bethesda, MD 20814.

News From Senior Physiologists

Paul W. Smith to John West:

A slight assist from a 51-year member of the Society is long overdue. [Letter accompanies a donation to APS.]

I have not been active in the affairs of APS since the 1940's, when I changed over into teaching and research in Pharmacology and became a member of ASPET. In the 1960's I changed again to become Director of a small research operation in Toxicology for the Federal Aviation Administration and retired from this position in 1977. These changes would scarcely have been possible without a firm background in Physiology, for which I have been ever grateful. Each of them, however, has brought a new allegiance and a new circle of friends and acquaintances, and something of an identity problem. I have missed my early friendships within APS.

I am in good health and maintain an active consulting practice in General and Combustion Toxicology. Thank you for the opportunity to be helpful.

1324 N.E. 56th St.
Oklahoma City, OK 73111

Ichiji Tasaki to Roy Greep:

Thank you very much for your letter. I am still working in the lab as usual. However, my interest has shifted from the peripheral nerve fiber (which had been my companion for good many years) to other parts of the nervous system. I agree with those who believe that the electrophysiology of nerve fibers, born in the middle of the last century, is now too old to be productive. During the past two years, I have been trying to gain information as to the mechanism of synaptic and sensory excitation by developing new optical, mechanical, and thermal sensors. This approach gives reasonable promise. I may be able to inform you new exciting results obtained by the use of my nonelectrical methods of investigation in the near future.

National Institutes of Health, Bldg. 36
Bethesda, MD 20205

Eugene P. Cronkite to Roy:

I have now attained the biblical three-score-and-ten and am fortunate that the Trustees of Associated Universities, Inc. renewed my scientific staff appointment through December 1985. I am also fortunate in being the recipient of an NIH research grant that goes for another 2 years and an NCI contract on radiation leukemogenesis that will continue for about 1–2 years. As long as I can still attract research funds and enjoy working, I have no intention of retiring. On the other hand, one should have enough common sense to realize that the time does come when one must give way for the advancement of younger individuals and turn over the responsibility to them.

Brookhaven National Laboratory
Upton, Long Island, NY 11973

Robert A. Cleghorn to Edward Adolph:

I am most grateful for the card you sent on behalf of the Committee on Senior Physiologists of the American Physiology Society conveying greetings on my 80th birthday. I well remember you giving a lecture in Toronto some 45 years ago and admire your continuing activity. It's no use to be idle, so I continue at our Sunnybrooke Hospital and try to keep up on hormones.

217 Glengarry Ave.
Toronto, Ontario M5M 1E3, Canada

Arnost Kleinzeller to Edward:

I greatly appreciated your warm wishes on my birthday and your welcome to the Senior Physiologists club. I must confess that I don't feel any older than I did a month or so ago. And at this stage I don't know what tired me out more – the protracted celebration *or* writing a competitive grant application. This second point should also answer what I am doing – I am enjoying the challenge of problems and hope to continue to do so for some time to come. And I remember fondly the warmth and friendship of you and colleagues when we came to Rochester in 1966.

University of Pennsylvania School of Medicine
Philadelphia, PA 19104

Donald Eaton Gregg (1902–1983

Donald Eaton Gregg was born in Bridgeport, Connecticut, the son of a minister. Most of his early years, however, were spent in the Finger Lake Region of Upstate New York. He liked to recount the memorable fishing ventures in the trout-laden streams and lakes. The memories of those years remained with him throughout his life. They provided him with a firm foundation and understanding of human values, and he liked to recall that what his family lacked in material wealth they gained in love and trust. He would relate how discretionary funds for the family remained in a jar from which all could borrow on an honor system. His early austere moral upbringing would later serve as a firm foundation for his illustrious career as a premier cardiovascular physiologist – a career based on the highest principles of integrity and scientific leadership.

Dr. Gregg followed his father to Colgate, graduating in 1924 Phi Beta Kappa with a B.S. in Chemistry. An early interest in integrating the biological and chemical disciplines was evidenced by his participation in both the biological and chemical societies on campus. His first career position was as a mathematics instructor at Northside High School, Corning, New York. He matriculated at the University of Rochester in 1926 and became a Porter Fellow. He earned his M.S. (1929) and Ph.D. (1930) degrees, submitting his doctoral thesis, on "Lipid Metabolism as a Possible Source of Carbohydrate."

In 1930 he entered the faculty of the Department of Physiology at Western Reserve, where his lifelong association with Dr. Carl Wiggers began. Those early years proved very trying with respect to starting a research career inasmuch as the great depression affected not only research funds but also faculty salaries. However, with belt tightening and maximum use of resources a full program went ahead. Initially, Dr. Gregg carried out his studies related to carbohydrate metabolism. However, after a few years he became caught up in the mainstream of Dr. Wiggers' laboratories.

Much of the work which was to thrust Dr. Gregg into the leadership role in coronary hemodynamics began to appear in the literature in the mid-1930's. His works included collaboration with Drs. Wiggers, Green, Eckstein, Fineberg, Mautz, Dewald, Thornton, Roberts, Wearn, and Pritchard (see *Coronary Circulation in Health and Disease*). These pursuits included definition of phasic right and left coronary blood flow, development of the orifice meter for recording blood flow, his pioneer studies on coronary artery collateral circulation, epicardial capacitance upon arterial flow, definition of coronary venous circulation, the concept that coronary arteries are not end arteries, the concept of peripheral coronary pressure, diastolic resistance, effects of coronary sinus ligation on the coronary circulation, and the determinants of coronary blood flow. Following this very important era of discovery and definition, Dr. Gregg devoted essentially the rest of his career confirming these early studies and refining them with the lastest technical advances. These initial studies became the foundation for coronary hemodynamic studies that continue today and remain the empirical references of excellence. One cannot pick out a study or group of studies and state that they represent the best, most significant, or the most important contribution(s) of Dr. Gregg. However, one must look at two papers in this era which defined the phasic coronary blood flows in the major right and left coronary epicardial arteries. The traces made with the differential manometers stand as the empirical references by which coronary physiologists still compare various flowmeter techniques to this day, and many textbooks still use illustrations based on Dr. Gregg's earliest recordings.

During the trying years of World War II Dr. Gregg continued studies with older associates mentioned above and with Book, Shipley, Rotta, Schroeder, Weisberger, Bidder, and Crittenden (see *Coronary Circulation in Health and Disease*). These studies included an attempt to define intramyocardial pressures at various levels in order to study the effect of that determinant on coronary blood flow at various myocardial levels during left myocardial systole. Dr. Gregg established that right coronary blood flow initially augmented upon acute elevation of pulmonary artery resistance; he observed similar left coronary responses upon increasing aortic resistances. He demonstrated that the anterior cardiac veins carried the venous return from the free right atrium and defined venous drainage of the various parts of the heart. He and his fellow associates published papers during this period defining peripheral blood flow in other organ beds, such as the brain.

After essentially establishing the field of coronary physiology, as we accept it today, Dr. Gregg left the faculty of Western Reserve as an associate professor in 1944. He returned to the University of Rochester to study medicine and earned his M.D. in 1946.

It is appropriate to look ahead a few years to relate the philosophy that lay behind Dr. Gregg's contributions to coronary physiology. He stated the following in his introductory talk, as Chairman of the International Symposium on Coronary Circulation and Energetics of the Myocardium, held in Milan in 1967.

"I believe we might all agree that the input disturbances that alter the coronary circulation and which we are most concerned with are those associated with everyday activity, i.e., physical exertion, emotional stimuli, and, possibly, hypoxia. If we consider the coronary flow as the output or the response of interest, then we know in a rather vague sort of way that this depends upon a combination of the geometry, structure and properties of the coronary blood vessels and the heart rate and blood pressure. We also know from the examples given and many others that there are multiple systemic and local control elements that influence the coronary flow. These include vascular receptors, the nervous system, endocrines, water, electrolytes, blood borne constituents, parenchymal activity and local metabolic products, autoregulators, and many others. But we do not know their proper weighting or significance or, indeed, that many of them actually obtain in the normal coronary circulation. We do not know what is the mechanism or the measuring device used to sense the need for flow and/or oxygen, nor how this is set, nor how information is transmitted to monitor the myriad of controlled elements.

"It is our hope that we are sufficiently intelligent and knowledgeable to interchange ideas and views so that we leave not with the fixed views with which we came but

with some new vistas and an eagerness to return to the laboratory where the answers are."

Dr. Gregg surrounded himself with intelligent hard-working, dedicated persons well trained in medicine and the basic sciences to help charge after those "answers."

In 1946 Dr. Gregg wrote the first of several reviews on coronary physiology. This year marked the beginning of his career-long association with the U.S. Army, having become the Chief Research Physician, Medical Research Laboratory, Fort Knox, with the responsibility for development of a basic research program in cardiovascular physiology. He remained in this capacity until 1950. During this period Dr. Gregg continued his investigations into appropriate techniques for monitoring coronary blood flow. He branched out into Fick methods in order to look into tissue blood flow in the myocardium. In his earlier studies with epicardial blood flow determinations he had warned fellow investigators that the phasic flow methods did not define the distribution of myocardial blood flow. In 1950 Dr. Gregg came to Walter Reed Army Institute of Research as Chief of the Department of Cardiorespiratory Diseases, the position that he maintained until his retirement in 1973.

In 1950 he published a very significant monograph *Coronary Circulation in Health and Disease* (Philadelphia, PA: Lea & Febiger, 1950), which remained the guiding authority in the field of coronary physiology for many years and may be looked at retrospectively as his operational mandate for the rest of his career and a guiding light for many coronary physiologists since that time. The following quotation from Dr. Wiggers' Foreword in the monograph accurately and beautifully describes the essence of Dr. Gregg's capabilities, temperament, and direction in unfolding the hemodynamic parameters of the coronary circulation: "It will be obvious to readers that Dr. Gregg has built his interpretations essentially around results obtained by use of adequate apparatus and techniques on normally beating hearts in the body. He recognizes that a study of the coronary circulation requires a synthetic as well as an analytic approach and that many special types of heart preparations were required as stepping stones toward a full understanding of the separate factors that control coronary flow. However, his own interest and that of his numerous associates have chiefly been directed toward the integration of these factors in the normally beating heart under diverse experimental conditions. If any criticism can be offered, it is that he has sometimes leaned too conservatively toward the side of caution. When doubt exists as to interpretations of his own work or that of others, he has frankly left an open opinon pending. But *how much better* than to err by speculating and theorizing on insecure or probable evidence!"

As Dr. Gregg took the reins of his department at Walter Reed, at what was then known as the Army Medical Service Graduate School, he really began a new career, one in which he not only conducted his own research but also became administratively responsible for many senior investigators. His mission enlarged, in that initially the Department of Cardiorespiratory Diseases had four distinct sections. Dr. Gregg continued to directly guide the fortunes of cardiovascular research, which focused its main emphasis on coronary hemodynamics. Other sections included pulmonary physiology, renal physiology, and the development of instrumentation particularly for cardiovascular studies. Dr. Gregg carried forth the philosophy of Dr. Wiggers in that he felt that a physiology department required its own tool shop with appropriately skilled personnel to operate such a unit. He had a great interest in fostering the development of pacesetting devices for experimentation, and he also felt the urgency of on-the-spot modification, where feasible, to foster a better, more "physiological model." From his shop emanated some of the unique devices, such as the miniature electromagnetic flowmeters, external terminals of various design and function, vessel occlusive cuff devices for low- and short-term utilization, which made possible much of the work that he and his associates accomplished in the second half of his career tenure at the Walter Reed Army Institute of Research.

Many Army officers who had just completed various levels of their medical training came to work with Dr. Gregg for as much as 3 years. As time went by several civilians with medical or basic science backgrounds associated themselves with Dr. Gregg for extended periods of time. One of his young officers remained in the Army for a career and subsequently undertook a leadership role in the department. Besides his own permanent staff of investigators one could always find a visitor or visitors from other laboratories and other countries coming to his laboratory for short or protracted visits. He always felt that such an influx of new blood prevented a sterile outlook and invigorated all with fresh ideas and new slants to old problems. During the 1950's Dr. Gregg's department became more consolidated and more firmly centered about cardiovascular research with, of course, center focus remaining upon the coronary circulation. He never forgot his early metabolic training and started a section in the department to pursue myocardial metabolism studies. Ultimately, he had hoped to tie in tissue metabolism with peripheral controls of coronary circulation. Of all the work coming out of Dr. Gregg's laboratories during this period, probably five studies have had a profound effect on the subsequent pursuits in coronary physiology. Sabiston and Gregg (*Circulation* 15: 14, 1957) showed that coronary blood flow increased 140% in the left coronary artery and 122% in the right coronary artery during asystole; this paper has been referred to many times both in the formal literature and in textbooks. In a second series, using the same type of anesthetized preparation, Dr. Gregg found that in the beating heart an increase of coronary perfusion pressure fostered an increase in the perfused myocardial tissue oxygen consumption. Such an observation defied "physiological reason" and has caused considerable controversy down to the present. The observation became known as "Gregg's Phenomenon," and Dr. Gregg dubbed it "Gregg's Folly." Present-day consensus substantiates the validity of Dr. Gregg's original observation. [An extensive and scholarly review of this subject appears in a recent paper in *Physiological Reviews* (63: 1–205, 1983) by Dr. Feigl.]

In the latter part of this period Drs. Coffman and Gregg published the first of several papers to come out of Dr. Gregg's laboratory defining myocardial reactive hyperemia, which subsequently has been used by many to describe the dilation capacity of the coronary bed. As a preliminary for future studies, Dr. Gregg and his associates published a technique paper that established a protocol for evaluating the metabolism of the left myocardium using left myocardial inflow and oxygen con-

tent of the coronary sinus. During this period extensive efforts were made to modify and miniaturize Dr. Kolin's design of the electromagnetic flowmeter. These studies did not represent the first conscious dog cardiovascular studies nor the first documentation of the coronary blood flow using the fast frequency response of the electromagnetic blood flowmeter.

However, the subsequent coronary hemodynamic resting, exercise, excitement, collateral, reactive hyperemia, sympathetic control, congenital hypertrophy and right coronary flow studies in the conscious dog confirmed the earlier studies of Dr. Gregg and his associates in Dr. Wiggers' laboratory and brought us closer to the true responses at rest and during stress. These studies, by Dr. Gregg and his associates at Walter Reed set the standards for other groups who published related studies using either the electromagnetic flowmeter or the ultrasonic flowmeter. With the development of the chronic canine preparation, Dr. Gregg studied the effect of complete neural ablation of the heart and its great vessels (the Cooper technique performed by Dr. David Donald) on the responses of the coronary circulation to the stresses of exercise and excitement. Shortly thereafter Dr. Gregg retired from active leadership because of Government rules regarding age limits for active service. However, this did not mean the end of his active participation in physiological pursuits; he appeared in his same office with the same frequency and duration as prior to his retirement. Even with the advent of new departmental leadership, the legacy of total scientific dedication that Dr. Gregg had built continued on, though with a shift of emphasis toward the relationship of adenosine analogues on the controls of peripheral coronary vascularization.

He continued to write, to attend selected symposia, and to discuss one of his favorite subjects, that of the collateral circulation of the coronary arteries. He continued to make his way to the Walter Reed laboratory until 1976 when the department he had started closed due to administrative decision made by the Army. He took up residency at the National Library of Medicine in a study which allowed him to be surrounded with his private collection of papers and books as well as the privileges of access to the overall library, thus providing him with the space to work on the sequel to his first monograph.

In January 1978 the Uniformed Services University of the Health Sciences appointed him Distinguished Professor of Internal Medicine and Physiology. Hence he began his active career teaching coronary physiology to medical students and graduate students. It only lasted for a short period, however, since his family felt that he should move to the Boston area so that he and his wife could be closer to their families. He continued to write his monograph on coronary circulation with the assistance of several associates and universities in the area, which generously offered space and facilities. Unfortunately, as his health began to deteriorate rapidly, he could no longer cope with the everyday stresses of urban living and retreated to his home to try to continue his writing. Ultimately, with the decline of his physical condition the opportunity for completion of his evaluation of present-day coronary physiology ceased.

Dr. Gregg's contributions to the literature spanned a 50-year period and included over 150 papers and reviews and sections within 10 books. He served on the editorial

President John F. Kennedy presents the President's Award for Distinguished Federal Civilian Service to Dr. Donald E. Gregg, Chief, Department of Cardiorespiratory Diseases, Walter Reed Army Institute of Research. The presentation took place on the White House South Lawn on August 7, 1962.

boards of several leading journals in his field, lectured, participated in professional study sections, and acted as a consultant to various functions within the Government. He attended many major symposia throughout the world and participated as chairman in several. He had gained an international reputation with great respect for his leadership in coronary physiology. He belonged to many professional societies including the American Physiological Society. Over the years many significant awards came Dr. Gregg's way, but most of all he cherished the Wiggers' Award from the APS and the President's Award for Distinguished Federal Civilian Service.

Dr. Gregg commanded the greatest of respect from his junior associates. He never demanded dedication or respect to himself, but certainly accepted no compromise for the dedication and respect to the task at hand. He did not have to assert his leadership, because he selected people, as dedicated as himself, who would puruse the scientific facts or methods that Dr. Gregg suggested or demonstrated and supported with technical personnel and material. Dr. Gregg accepted no compromise in the pursuit of scientific fact. When he requested information, the reply required an exacting definitive answer. He proved masterful at conveying his pleasure or displeasure with ongoing situations using many indirect modes of communication, such as hyperbole. He never tolerated procedures that interfered with scientific progress. He had a formal office, but his real office resided in Room 38 (Walter Reed Institute of Research). There among his private journal collection, endless collection of strip charts, and piles of illustration boards from past papers he conducted his quest into the mysteries of coronary physiology. This austere room had a long table and two hard-back chairs that he would use and an old green stuffed leatherette chair reserved for visitors to "his" office-study. Once he politely ushered a visitor to that green chair, one would seldom know the direction or duration (he never had a keen sense of time's passing) of such an encounter. He never would knowingly humiliate or challenge a person; he could and would by methods of reason try to steer away from the trivial, unreasonable, or nonproductive. He enjoyed exploring untested ground or raising provocative scientific points. He could

convey messages in many subtle forms, and many a time one would only realize the "real" theme after leaving Dr. Gregg. Cloistered within his scientific sanctuary, this man of great studies and papers agonized over his writing, always wondering if what he stated on paper conveyed the message he intended.

As stern and uncompromising as he seemed with regard to scientific dedication, Dr. Gregg was a very warm and loving individual to those who knew him well and understood him. He loved children and showed great interest in the well-being of the families of his staff. This man with the reserved, taciturn, austere countenance did exude a warm loving side to his fellow associates, for he had compassion and desire to impart help and understanding not only to those of high seniority in his laboratory but also to those of lesser standing whom he respected for what they did for his science. Not only did he show compassion for all humans in his charge but the appearance of steak bones in the cages of our dogs bespoke his concern for them, too.

To review subsequent accomplishments of the many who came to Dr. Gregg's laboratory would unfold a gazeteer of no small proportions of leaders in medicine, research, and other allied fields today. Although this one distinguished leader in physiology has finished his service, many of his disciples carry forth his high principles today; Dr. Gregg felt a great sense of satisfaction and pride to see his people move forward and forge their own successful careers.

We who had the privilege of working in Dr. Gregg's laboratory look on him with a love held for one's father, in this case our professional or career father. Not only did Dr. Gregg serve the overall Society in the highest of traditions, but he, in essence, served his junior associates by the scientific heritage he bestowed upon us.

H. S. Lowensohn and R. A. Olsson

Emma Bockman (1946–1985)

Emma L. Bockman, former member of the American Physiological Society, who served for the past three years on the Membership Committee, died 1 March 1985. She was known and respected by the research community in the field of metabolic control of blood flow, where her work contributed significantly to the understanding of blood flow to red versus white skeletal muscle types and blood flow in adipose tissue. Emma's dedication to teaching was felt by all students who were fortunate enough to experience her socratic methods of teaching. She continuously strived for excellence in research and teaching. All of us fortunate enough to have known Emma have had our lives enhanced. We have lost a valuable friend and colleague, but in her memory we must attempt to keep her academic ideals and search for knowledge alive. A memorial fund for graduate research in the area of cardiovascular and cancer investigation has been set up in the name of Dr. Emma L. Bockman. Contributions should be sent to the Henry M. Jackson Foundation—Emma Bockman Memorial, 4301 Jones Bridge Rd., Bethesda, MD 20814-4799.

Alberto Hurtado (1901–1984)

Alberto Hurtado was born in Lima, Peru in 1901. He entered the Universidad Nacional Mayor de San Marcos of Lima in 1918 and obtained the B.Sc. degree in 1920. Because of political problems, San Marcos was closed by the government that year and Hurtado moved to the United States. He was admitted to Harvard University School of Medicine, which kept an exchange program with San Marcos. In 1924 he obtained the M.D. degree, and in 1925–26 he was an intern at the Boston City Hospital. He returned to Peru in 1928 and joined Carlos Monge M. in a classical expedition to the Peruvian Andes, which resulted in disagreement with the Cambridge (England) physiologist, Joseph Barcroft, who did not believe in human acclimatization to high altitude. Barcroft had organized an expedition to Cerro de Pasco, Peru in 1921, and from his book *Lessons from High Altitude* arose a world interest in the subject. Under a Rockefeller Foundation fellowship, Hurtado returned to the US and joined the distinguished group of pulmonary physiologists at the University of Rochester in New York from 1931 to 1934. Back in Peru in 1935, he became Professor of Physiopathology, Director of the Institute of Andean Biology, and Dean of the Medical School at San Marcos. In 1961, Hurtado reacted against the excessive politicization of his University and lead a massive resignation of about 400 professors from the School of Medicine. Immediately after, he created the Cayetano Heredia University of Lima, whose School of Medicine soon became one of the most prestigious medical institutions of Latin America. He became the first Dean of Medicine and later its Rector.

This adventurous academic and administrative life was enough to give Hurtado an international reputation. This indefatigable man maintained, in addition, a leadership in the field of high-altitude research. For this he received a Doctor Honoris Causa degree from four different institutions: the University of Rochester in New York, from the Cuzco and Arequipa Universities of Peru, and the National University of Chile. He was also awarded the Honorary Membership by the American College of Physicians and the American *Physiological* Society.

Hurtado's greatest recognition came when he was awarded the first Bernardo Houssay Prize in 1972. His classical article in the *Handbook of Physiology* in 1964 and the Ciba Foundation Symposium, held in London in 1971 in his honor, are permanent sources of reference.

The author of this note will always remember those student years spent at Hurtado's laboratory where experiments began at 5:30 A.M. and were only interrupted to attend classes, returning to the laboratory very often late at night. The young team of medical students then moved to the Morococha Laboratory at 4,500 m to repeat the studies on high altitude with native volunteers. Professor Alberto Hurtado can be considered as the best example of "reverse brain drain." None of his early associates have left Peru for other countries.

C. Monge C.

Statistics on APS Membership (As of February 1985)

Total Membership 6249

Distribution by Employment*

	No.	%
Medical Schools	3672	65
Physiology Departments	(1915)	(34)
Other Preclinical Departments	(464)	(8)
Clinical	(1243)	(22)
Administration	(50)	(1)
Hospitals and Clinics	241	4
Veterinary Schools	111	2
Dental Schools	50	1
Public Health and Graduate Schools	197	4
Undergraduate Schools	489	9
Commercial Companies	119	2
Government	343	6
Institutes and Foundations	213	4
Private Practice	47	1
Other, Emeritus or Inactive	124	2

*5,606 Respondents

Distribution by Earned Degree*

(Includes 685 individuals with multiple doctorate degrees)

	No.
Ph.D.	3865
M.D.	2216
D.V.M.	138
D.D.S. and other	27

*5,559 Respondents

Principle Type of Work*

	%
Research	71
Teaching	15
Administration	7
Clinical	6
Other	1

*5,608 Respondents

Distribution by Primary Specialty*

	%
Cardiovascular	21
Neurophysiology	12
Respiration	10
Endocrines	9
Renal	6
Muscle and Exercise	5
Electrolyte and Water Balance	5
Gastrointestinal, Food and Nutrition	4
Cellular and Tissue	3
Environmental	3
Comparative	3
Blood	2
Energy Metabolism and Temperature Regulation	2
Pharmacology	2
Reproduction	2
All Other Categories (None above 1%)	9

*5,494 Respondents

Distribution by Age*

	No.
70+	591
60-69	996
50-59	1606
40-49	1858
30-39	1074
20-29	58

*Optional personal data (numbers represent total respondents)

Distribution by Sex*

Female	671
Male	5359

*Optional personal data (numbers represent total respondents)

States in U.S. with more than 100 Members*

California	662	Florida	162
New York	616	New Jersey	160
Texas	362	North Carolina	158
Pennsylvania	319	Missouri	136
Maryland	314	Virginia	130
Massachusetts	309	Connecticut	121
Illinois	293	Minnesota	115
Ohio	224	Wisconsin	106
Michigan	176	Tennessee	101

*50 States plus Puerto Rico and Virgin Islands

Distribution by Racial Background and Heritage*

American Indian or Alaskan	7
Asian or Pacific Islander	253
Black	33
White	4269
Hispanic Heritage	82

*Optional personal data (numbers represent total respondents)

APS North American Membership

United States	5841
Canada	251
Mexico	7

Canadian Provinces with 5 or more Members

Ontario	99
Quebec	63
Alberta	25
Manitoba	21
British Columbia	20
Nova Scotia	10
Saskatchewan	9

Other provinces represented:
- New Brunswick
- Newfoundland
- Yukon Territory

APS Membership Outside North American

Countries with 5 or more members:

Japan	31
United Kingdom	27
Germany, Federal Republic	25
Switzerland	18
France	12
Sweden	10
Israel	9
Australia	8
Italy	7
Denmark	7
Spain and Canary Islands	7
Netherlands	7
Venezuela	6
Belgium	6
Norway	5

Other countries represented:

Argentina	Nigeria
Austria	Panama
Brazil	Paraguay
British West Indies	Peoples Republic of China
Chile	Peru
Dominican Republic	Poland
Finland	Portugal
Greece	South Korea
Hong Kong	Rhodesia
Hungary	Saudi Arabia
Iceland	Singapore
India	South Africa
Jamaica	Taiwan
Kuwait	USSR
Lebanon	Yugoslavia
New Zealand	

ASSOCIATION OF CHAIRMEN OF DEPARTMENTS OF PHYSIOLOGY
ANNUAL QUESTIONNAIRE - 1984/85

B. Type of Institution:

Physiology Department primarily in a MEDICAL (94½) or NON-MEDICAL* (8½) school.
* Specify type of school: _____

Primary affiliation: PUBLIC (63) or PRIVATE (35). (5 N/A) Total - 103

C. Numbers of faculty with academic appointments (regular or joint) in your department:

SUM = TOTAL = SUM

	Degree(s) Held				Number of Faculty		
	Ph.D.	M.D.	Both	Other		Tenured	Not Tenured
Entire salary through your department:							
Full time	1,104	97	57	42	1300	852	448
Part time	42	13	3	9	67	30	37
Part of salary through your department, and associated with:							
another basic sci. dept.	44	16	3	2	65	31	31
a clinical dept.	65	15	3	4	87	40	27
other	4				4	2	2
No salary through your department, and associated with:							
another basic sci. dept.	147	17	6	4	178	95	52
a clinical dept.	157	158	25	8	348	157	132
other	1				1	1	
Other (Emeritus, volunteers, etc.)	157	41	26	9	234	44	118

D. Unfilled Positions:

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

Professor 10 Assistant Professor 58

Associate Professor 17 Instructor 7

Unspecified Rank 7

How many of the unfilled positions are due to:

Creation of new FTE's 25 Failure to promote/tenure? 14

Death? 4 Creation of new FTE's? 6 Other 34

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

yr. 1 52 yr. 2 41 yr. 3 40 yr. 4 23 yr. 5 29

E. Current Graduate Students and Postdoctoral Fellows:

Number of graduate students currently enrolled in Department Ph.D. Program 1329

Number of Postdoctoral Fellows currently in your Department 534

Number of vacant Postdoctoral positions 64

F. Training Support:

Do you have a training grant that supports predoctoral trainees? YES (36) NO (64)
Do you have a training grant that supports postdoctoral trainees? YES (32) NO (65)

	Predoctoral	Postdoctoral
What is the average starting stipend for trainees?	$6600	$15,634

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

Training grants?	177	89
Individually federally funded awards?	32	88
Research Grants?	248.5	130
State funds?	280.5	14
Private foundations?	34	48
Institutional awards?	221	15
Medical Scientist Training Programs?	46	2

Other? List: 93

G. Number of trainees who have finished Doctoral or Postdoctoral work during the year ending June 30, 1984:

	Doctoral	Postdoctoral
Total number finishing:	135	130
Females	42	24
Blacks	3	2
Other Minorities	7	20
Position needed	2	1
Research Area:		
Cardiovascular	47	44
Cell/Tissue	34	15
Comparative	2	1
Endocrine	50	21
Environmental	8	2
Gastrointestinal	6	9
General	3	1
Muscle/Exercise	6	3
Neural	32	26
Renal	9	3
Respiratory	12	2

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

Very Pleased (10) Pleased (47) Neutral (25) Disappointed (3)

Very Disappointed (0)

How many postdoctoral students are presently taking additional training because they are unable to find a satisfactory position? 36

PART II - Confidential information which will not be identified by institution.

A. Faculty Salaries for Fiscal Year 1984-1985.

Please indicate the salary level per year of full-time faculty based in your Department for each rank. Please include unfilled positions.

Chairman's Salary: $74,198 Number of Years in Position 9.2 (Avg.)

(Put one numeral per space, expressing salary in whole dollars.)

Professor Salary	Assoc. Prof. Salary	Assist. Prof. Salary	Instructor Salary
$54,529	$41,884	$32,544	$22,319

B. Departmental Budget for Fiscal Year 1984 - 85 (Salaries and Operation):

1.	Institutional Sources	$745,797
2.	Outside Research Grants	970,343
3.	Training Grants	133,018
4.	Other Budget Support	145,578

Identify "Other":

_____

_____

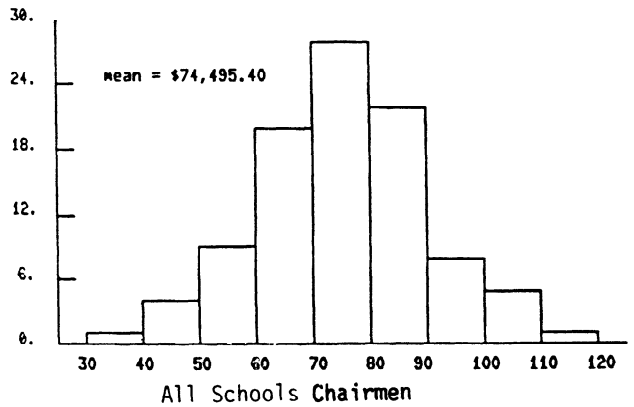
_____

TOTAL $2,035,566

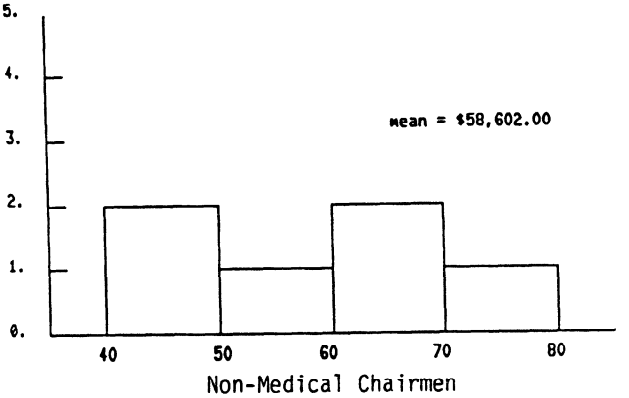
C. Space Assigned to your Department (excluding lecture rooms):

Research	9604	(square feet)
Teaching Labs	4080	
Other	4758.9 (Office/Storage Space)	
TOTAL	19,349	

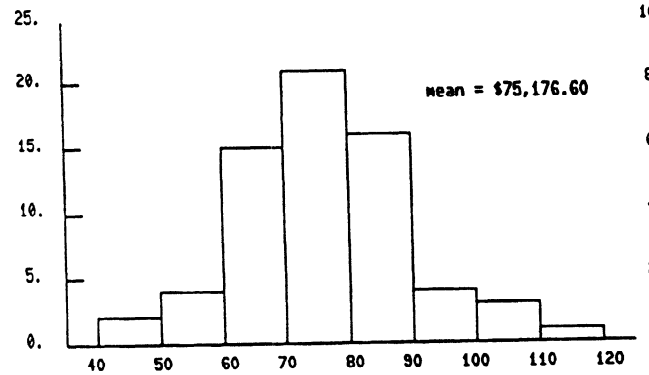
FACULTY SALARIES in thousands of dollars



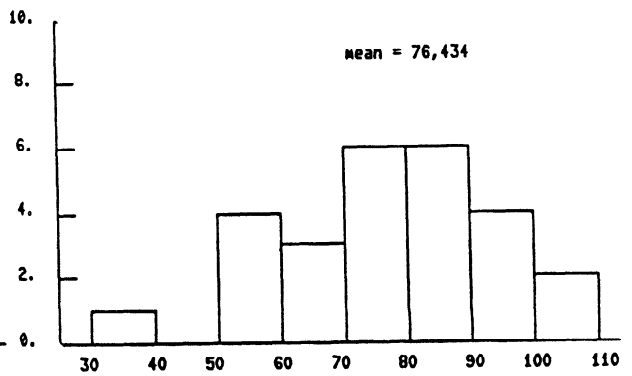
All Schools Chairmen



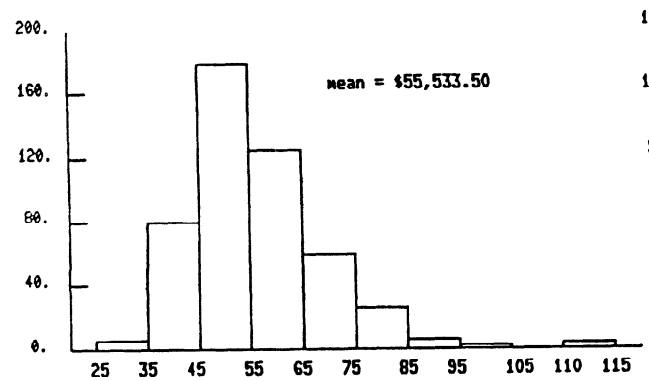
Non-Medical Chairmen



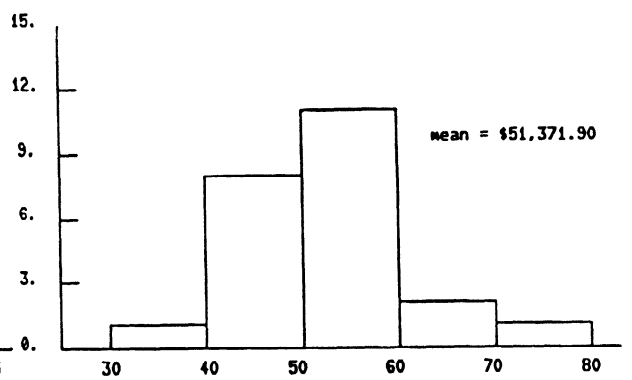
Public Medical Chairmen



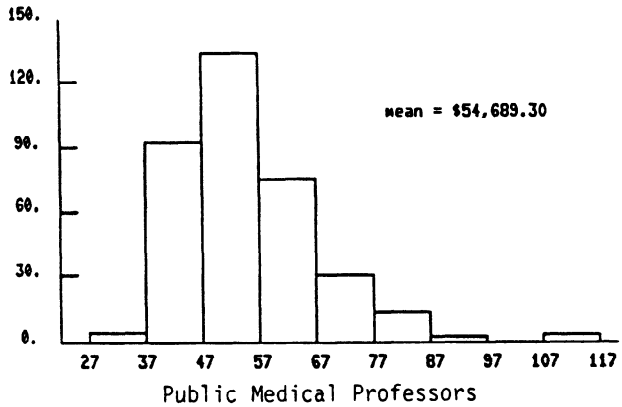
Private Medical Chairmen



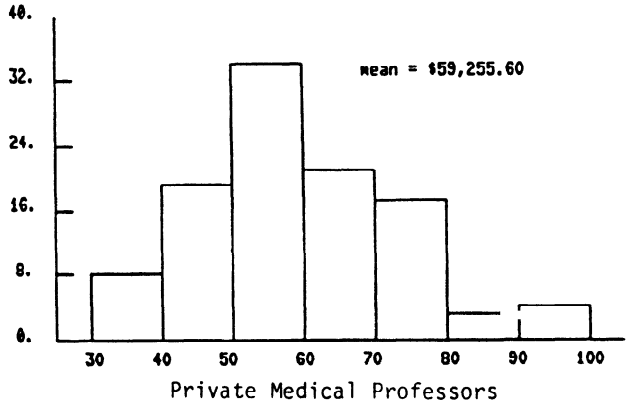
All Schools Professors



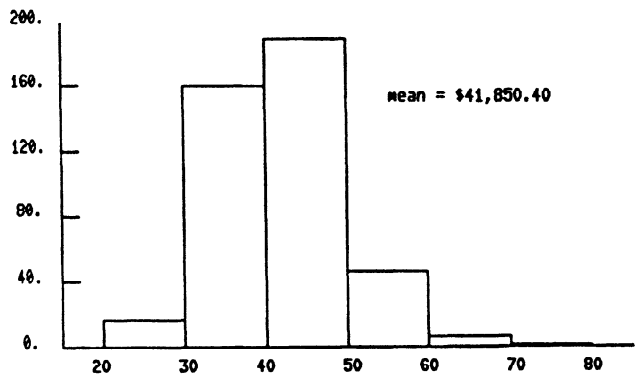
Non-Medical Professors



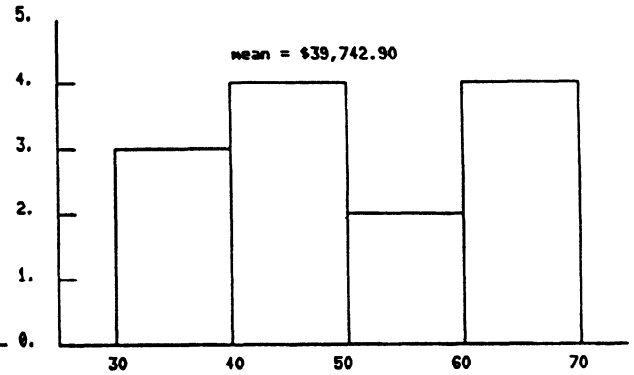
Public Medical Professors



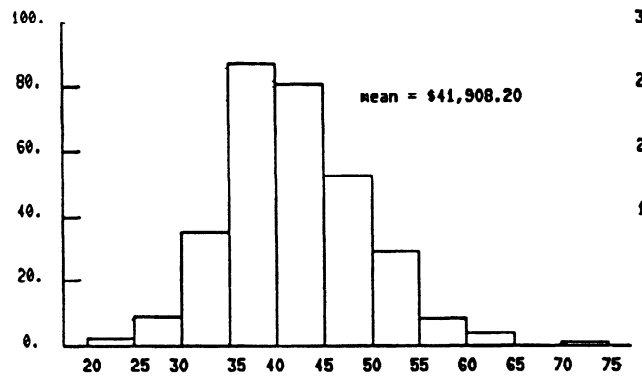
Private Medical Professors



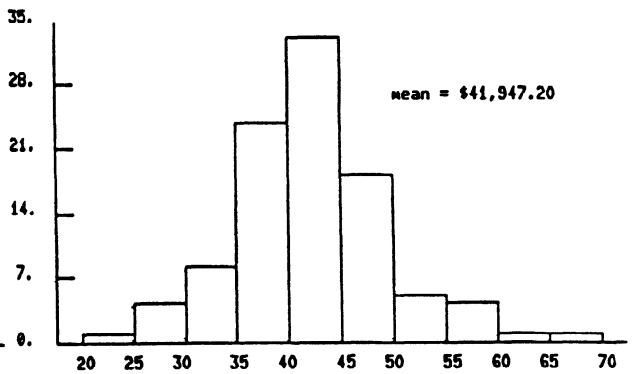
All Schools Associate Professors



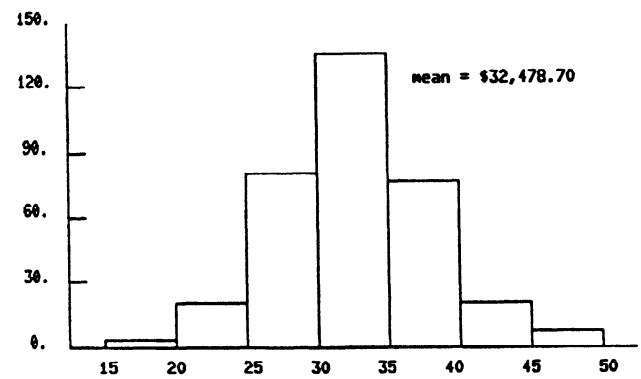
Non-Medical Associate Professors



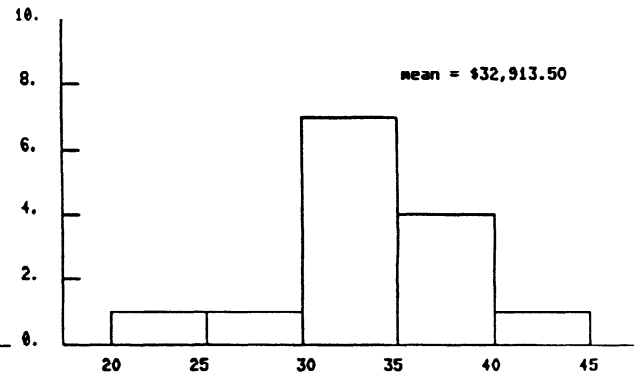
Public Medical Associate Professors



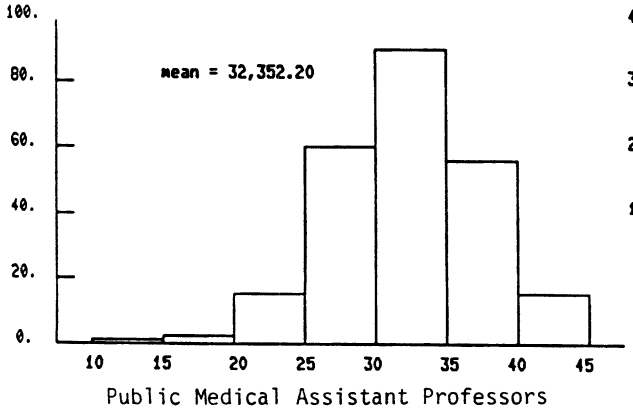
Private Medical Associate Professors



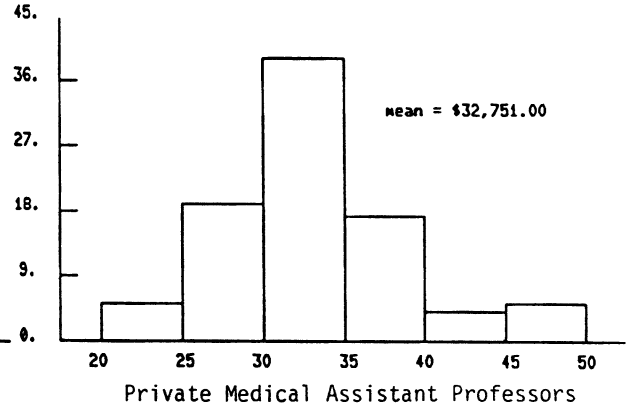
All Schools Assistant Professors



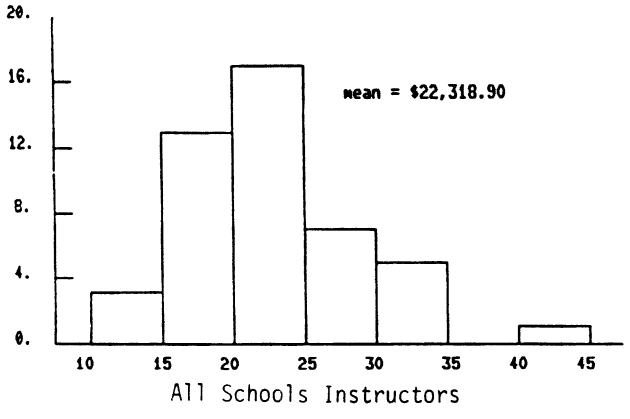
Non-Medical Assistant Professors



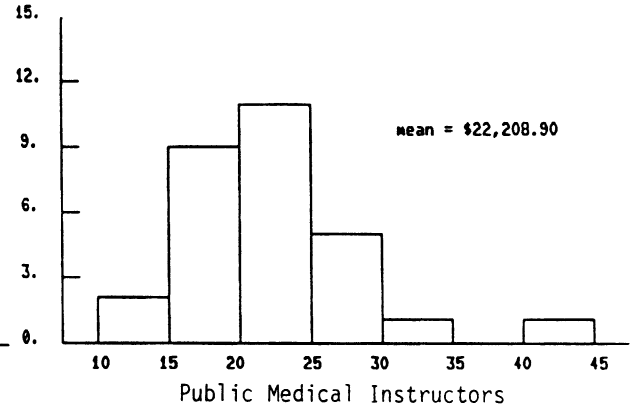
Public Medical Assistant Professors



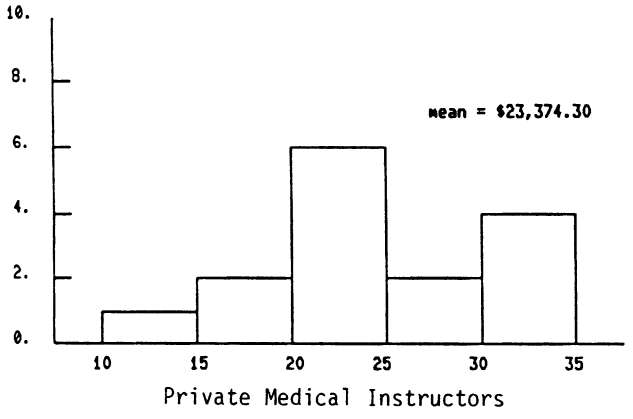
Private Medical Assistant Professors



All Schools Instructors



Public Medical Instructors



Private Medical Instructors

	Average Salary				
	Chairman	Professor	Associate Professor	Assistant Professor	Instructor
Public Medical School	75,176	54,889	41,908	32,352	22,208
Private Medical School	76,434	59,255	41,947	32,751	23,373
Non-Medical School	58,602	51,371	39,742	32,913	16,000

Cellular Alterations in Shock and Ischemia and Their Correction

IRSHAD H. CHAUDRY
Department of Surgery
Yale University School of Medicine
New Haven, Connecticut 06510

For the purpose of this article, shock will be considered a syndrome that results from inadequate blood flow to vital organs or the inability of the body cell mass to metabolize nutrients normally. Thus shock and all its ramifications result from a sustained reduction in perfusion of capillaries and therefore of tissues and organs. Major operations, trauma, myocardial diseases, and severe infection all may lead to circulatory failure or shock. Along with these, atherosclerosis, repair or transplantation of an organ, or vessel injury may lead to ischemia of an organ or various organs. Thus what happens to an organ with regard to function of its component cells and what happens to the cell of an organ with sufficiently diminished flow becomes a critical series of events in terms of survival of the organ and the individual. As a result of prolonged reduction in tissue perfusion, various alterations in tissue metabolism, structure, and function occur at the systemic, cellular, and subcellular levels.

Although all adverse conditions that produce decreased circulating volume would eventually cause alterations in cellular and subcellular function, the changes occurring as a result of hemorrhagic shock will be specifically addressed here. In addition, we will discuss the possible ways by which such lesions could be corrected. Abnormalities following trauma, sepsis, and surgery will not be discussed, but pertinent references will be provided (10).

The acute loss of circulating blood volume, with or without mechanical tissue trauma, initiates an intensive neurohormonal activation. Although compensatory mechanisms (1, 6) are adequate in the acute stage of hypovolemia, sustained vasoconstriction with release of various vasoactive agents may result in hemodynamic and microcirculatory alterations.

Alterations in Mitochondrial Metabolism

We will now deal with the alterations in mitochondrial metabolism during shock. Studies of mitochondrial metabolism have been conducted by isolating mitochondria from tissues of animals at various stages of shock or ischemia (7). It should be pointed out, however, that such in vitro studies do not directly indicate the capability of the mitochondrial in situ during these conditions, since the process of isolation may itself alter the preexisting capabilities of the mitochondria. Nonetheless, additional studies have confirmed that the changes in mitochondrial capability observed in vitro do indeed take place in vivo in animals during shock.

Before we discuss the mitochondrial changes during shock, let us review the parameters used to measure mitochondrial function. When oxygen, inorganic phosphate, and adequate substrates are provided to normal mitochondria in vitro, they respond to additions of adenosine 5'-diphosphate (ADP) by increasing their rates of respiration to a maximal level. The ratio of this stimulated rate to the basal rate, i.e., the respiratory control ratio (RCR), is thus a more critical measure of the integrity of mitochondria than the ADP:O, which is a test of phosphorylation efficiency alone. A normal ADP:O would indicate that some oxidative phosphorylation is taking place and is therefore a crude measure of the mitochondrial function. Thus it could be suggested that the RCR is a more critical measure of the integrity of mitochondrial function.

It is well recognized that mitochondrial electron transport-linked reactions provide almost 95% of the body's energy needs under normal conditions. To perform this function, however, the mitochondria utilize >90% of the available cellular oxygen. It is thus obvious that any abnormality in mitochondrial function due to the lack of oxygen, to defects in electron transport-linked carriers or enzymes, or to the lack of substrates would be expected to have a deleterious effect on the cellular energy supplies.

Measurement of liver mitochondrial function at various stages of hemorrhagic shock with succinate as a substrate indicated that there is a progressive but very small decrease in the capability of mitochondria to use suc-

CME Category I Credits

With the February issue of *The Physiologist* [28(1): 47, 1985] began an APS Education Committee program of publishing reviews of recent advances in physiology aimed specifically at physicians seeking to keep abreast of current research in a wide variety of fields. These review articles are accompanied by a set of questions, the submission of which will enable physicians to earn Continuing Medical Education Category I Credits. Of course, it is our hope that these papers will be of use and interest to all teachers and students of physiology whether or not they are physicians.

It is the intention of the American Physiological Society to also publish these reviews as audiocassette tapes for distribution to a wider audience than will be served by *The Physiologist.*

These papers have been solicited from outstanding experts in a wide variety of biomedical research areas and have been edited to yield clear and concise reviews of topics in physiology of wide interest. The Editorial Board responsible for assembling these papers consists of Joel A. Michael (Chairman), Rush Medical College; L. Arthur Campfield, Northwestern University; Neil Kurtzman, University of Illinois; James Houk, Northwestern University; and Allen A. Rovick, Rush Medical College.

cinate. With α-ketoglutarate, however, the magnitude of the decrease in mitochondrial RCR was significantly more. This suggested that the α -ketoglutarate system was more sensitive and susceptible to insults than was the succinate system. The reasons for this are apparent by looking at the diagram of the glycolytic pathway, the tricarboxylic acid cycle, and the electron transport system in Figure 1.

As can be seen from Figure 1, succinate enters directly from the tricarboxylic acid cycle into the electron transport chain, whereas α-ketoglutarate goes into the electron transport system from the tricarboxylic acid cycle through a more complex mechanism involving nicotinamide adenine dinucleotide (NAD) and coenzyme A (CoA). This may be the reason for the marked depression in mitochondrial metabolism observed with α-ketoglutarate compared with succinate. Studies have, in fact, shown alterations in the α-ketoglutarate metabolism in the absence of changes in succinate oxidation in the liver mitochondrial when *Escherichia coli* endotoxin was added in vitro. Regardless of the differential sensitivities of substrates, the information available at present clearly indicates that a severe and progressive defect in liver mitochondrial metabolism occurs in shock and that this is reflected by the significant decrease in RCR. It is thus apparent that, after shock or ischemia, mitochondria cannot respond to energy needs by a normal acceleration tion of oxidative phosphorylation even though oxygen, substrate, and NAD are provided. Thus the functional capacity of mitochondria is altered during shock and low-flow conditions.

The question that should be raised, however, is what is the reason for the depressed mitochondrial metabolism in shock and ischemia. The lowered respiratory parameter in shock with NAD-linked substrates could be due to *1*) an alteration in the relationship among NAD, the multienzyme nature of the system, and the electron transport phosphorylation system, which is indicated by the decrease in substrate oxidation; or *2*) an alteration in coupling between phosphorylation and oxidation through electron transport, which is indicated by the decrease in RCR. Since a small change in succinate RCR is observed during shock, the first explanation is more appropriate than the second but does not exclude uncoupling with α-ketoglutarate. The precise mechanism by which shock produces such alterations is not known, although anoxia appears to be an important factor.

In addition to the above, several other factors may be responsible for the alterations in mitochondrial metabolism during shock. These include *1*) structural changes in mitochondria; *2*) alterations in the enzyme system by the loss of cofactors due to mitochondrial swelling, loss from the mitochondria, or failure to recycle due to decreased available energy; *3*) decreased mitochondrial magnesium levels; *4*) increased mitochondrial calcium levels; *5*) extramitochondrial inhibition by factors such as free fatty acids; and *6*) free radical oxidation of mitochondrial phospholipids.

Mitochondrial and cellular ultrastructural changes have been demonstrated after prolonged hemorrhagic shock, and these include swelling of the mitochondria and disruption of the intramitochondrial structure. It has also been shown that several cofactors do indeed leak from cells during shock and ischemia. Thus loss of cofactors from the mitochondria or failure to recycle them may also be a cause for the depressed mitochondrial function in shock.

A significant decrease in the state 3 and the RCR of liver mitochondria from animals in late hemorrhagic shock was observed by using both α-ketoglutarate and β-hydroxybutarate. The fact that the RCR changes with both of these substrates were primarily due to decline in state 3 respiration suggests that mitochondrial respiration becomes limited by changes at the terminal steps, i.e., the activity of the dehydrogenase, and not by changes inside the respiratory chain. Since NAD is required for both the α-ketoglutarate and β-hydroxybutarate dehydrogenase activities, the loss of this cofactor from liver mitochondria of animals in shock could be responsible for the decline in state 3 respiration with these substrates.

Another factor that may be responsible for inhibition of mitochondrial function during shock is magnesium, since it is required for synthesis of cofactors such as coenzyme A and thiamine pyrophosphate. A rise in plasma magnesium that could very well be related to a deficiency in cells has been shown to occur during shock. Although the overall alterations in mitochondrial magnesium have been found to be small during shock, it was noted that the magnesium that exists in the mitochondria, primarily in the bound form, was more labile. Thus it could be

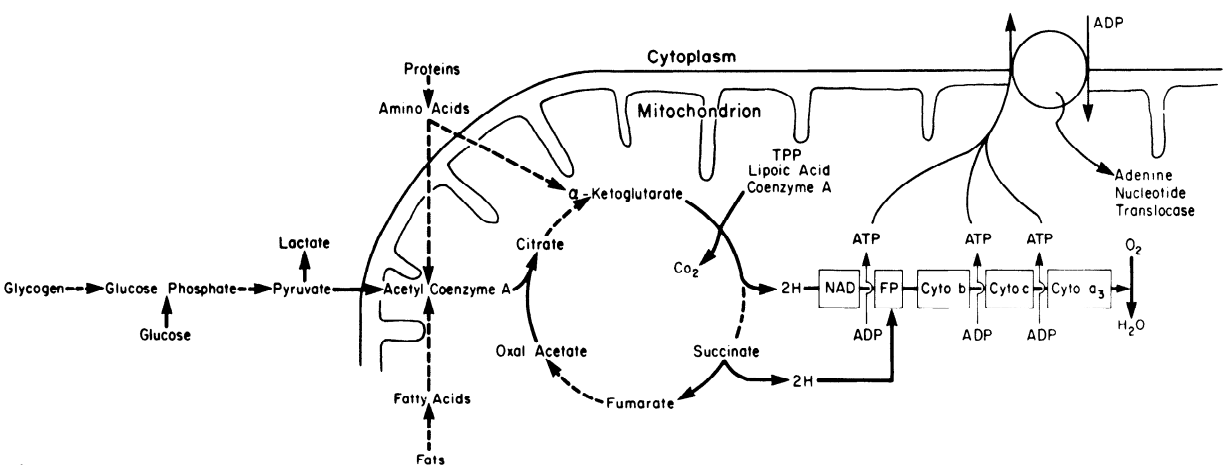


Figure 1
Glycolytic cycle, tricarboxylic acid cycle and electron transport system.

suggested that mitochondria in shock lose their ability to maintain bound magnesium and that this is a signal for impaired membrane structure, reflected by the mitochondrial swelling and other alterations described above. The magnesium deficiency itself may cause a significant inhibition of the α-ketoglutarate oxidation.

Mitochondrial calcium levels have also been found to increase after shock and ischemia and high levels of calcium are known to produce loss of mitochondrial function. This may therefore be another factor responsible for the decreased mitochondrial function in shock and ischemia. However, influx of calcium may well be a late manifestation of cell swelling resulting in inhibition of mitochondrial production of adenosine 5'-triphosphate (ATP).

It is also possible that the increased mitochondrially associated free fatty acids may be responsible for inhibition of mitochondrial function during shock. Studies have shown that hepatic mitochondrial free fatty acid levels increase progressively after ischemia and reflow.

It has also been suggested that free radical oxidation of mitochondrial phospholipids may occur during ischemia and that alterations in lysosomal enzyme activities occur simultaneously with the mitochondrial alterations. It is not known, however, whether these extramitochondrial alterations can also secondarily damage mitochondrial membranes. Nonetheless, the fact remains that mitochondrial metabolism is adversely affected, perhaps by a number of mechanisms, and this effect is progressive with the severity of shock.

Shuttle Mechanisms

Let us now discuss the shuttle mechanisms and whether they are affected in shock. The inner mitochondrial membrane itself is considered to be impermeable to adenine nucleotides. As can be seen in Figure 1, energy-linked shuttle mechanisms exist for the translocation of ATP from the intramitochondrial site of oxidative phosphorylation to the cytoplasm, and ADP and inorganic phosphate must be returned to the mitochondria for resynthesis of ATP. Lactic acid is formed in the cytoplasm as the end product of anaerobic glycolysis; reducing equivalents must be transformed into the mitochondria if complete oxidation of the lactic acid is to occur. In the absence of this, lacticacidemia will result. This process in normal conditions is accomplished by the complex malate-aspartate shuttle (Figure 2) in which malate and glutamate are translocated into the mitochondria while 2-oxoglutarate and aspartate are transferred out. However, the functioning of different isoenzymes of both aspartate aminotransferase and malate dehydrogenase in the cytoplasm and in the mitochondrion is essential for the operation of the shuttle. It has been shown that mitochondrial aspartate aminotransferase of liver origin is present in the blood during hemorrhage and that serum levels of malate dehydrogenase, another enzymatic component of the malate-aspartate shuttle, are significantly increased after hemorrhagic shock. The intramitochondrial activity of this enzyme has been shown to decrease significantly in the liver at intervals following injury, and thus the activity of this shuttle would be expected to decrease under such conditions. Studies have, in fact, suggested aberrations in malate-aspartate, carboxylic, and perhaps other shuttles as well during shock.

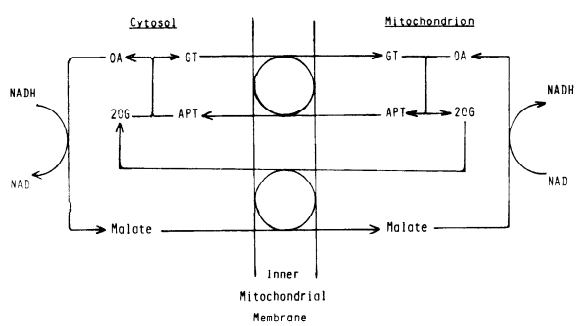


Figure 2
Malate-aspartate shuttle. OA, oxaloacetate; GT, glutamate; 2OG, 2-oxoglutarate; APT, aspartate.

Mitochondrial Cation Alterations

Since alterations in metabolic capability as well as morphology and swelling of mitochondria occur during shock, intramitochondrial contents of water and cations might be altered with the shock process. Studies have shown significant alterations in sodium and potassium content of mitochondria that are progressive with the severity of shock. The alterations in calcium and magnesium have already been described. Thus the information available indicates that severe hemorrhagic shock in rat liver mitochondria is characterized by a great increase in sodium and calcium and by a decrease in potassium and by an increase in the lability of magnesium. It would therefore appear that there are alterations in cation and water within the cell that also involve the mitochondria.

Reversibility of Hepatic Mitochondrial Dysfunction

A question that should be raised is whether the mitochondrial alterations are reversible. In this regard, it has been shown that returning the shed blood even in the early stages of shock does not improve mitochondrial respiratory activity. However, the administration of Ringers lactate solution plus blood has been shown to restore the mitochondrial parameters to near normal levels. Whether this is due to the increased volume of fluid given to improve the circulation in early shock or to the longer period allowed for improvement is not known. However, the fact remains that mitochondrial dysfunction with α-ketoglutarate can be reversed with increased fluid treatment in the early stages of shock. With severe shock, however, the depressed mitochondrial metabolism cannot be reversed simply by returning the shed blood. This is due to the fact that a prolonged lack of oxygen induces reduction of the respiratory chain components and cessation of electron flow, and thus mitochondrial metabolism will be expected to remain depressed. Nonetheless, if the mitochondrial membranes are not permanently damaged, replenishment of oxygen supply and substrate should reactivate electron transport and utilization of oxygen and substrates. Mitocondrial membranes are, however, sensitive to prolonged ischemia, and eventually permanent damage to mitochondrial membranes occurs if ischemia continues beyond a critical period. The exact length of this critical period is not known at present.

Mitochondrial Function in Other Organs and Tissues

Another question that should be raised is whether alterations in mitochondrial function occur in all tissues and organs during shock. In this regard, although some studies have indicated that mitochondrial dysfunction does not occur in the lungs, brain, or heart of animals in hemorrhagic shock, mitochondrial dysfunction in the above organs may well occur under other circumstances. In view of the fact that cerebral circulation is maintained at the expense of other vascular beds, e.g., splanchnic, it would appear unlikely that brain mitochondrial function should decrease in hemorrhagic shock until near death. Whether or not there are mitochondrial changes in cells of a certain tissue or organ is probably determined primarily by circulatory priorities and distribution of cardiac output and blood flow rather than by any characteristics of that tissue.

Metabolic Alterations in Shock

The next issue we will address is whether there are metabolic alterations in shock. There is a progressive accumulation of many metabolites in blood during shock, suggesting both increased breakdown and failure of anabolism in the tissues. Free fatty acid levels have been shown to increase and almost all circulating amino acids also increase in concentration. The depressed mitochondrial redox potential during shock would also cause a decrease in the ratio of cytoplasmic NAD (NAD:NADH) to the reduced form. Since NAD is required in the oxidative decarboxylation of pyruvate to acetyl-CoA and NADH is required for the reduction of pyruvate to lactate, a decrease in the cytoplasmic NAD:NADH during shock reduces the rate of pyruvate conversion to acetyl-CoA. Thus lactate production increases; this results in an increase in lactate-to-pyruvate ratio and acidosis becomes progressively more severe. There is also a biphasic change in serum glucose with an early hyperglycemia that progresses to hypoglycemia toward the final phase of the shock period.

Alterations in Cellular Nucleotide Levels

A common feature of all forms of shock is an inadequate circulation with a diminishing blood flow to the tissues. Since a major portion of the oxygen required in tissue metabolism is used for the generation of high-energy phosphate bonds by the process of oxidative phosphorylation, it would be expected that the level of high-energy phosphate compounds such as ATP should decrease in tissue as tissue hypoxia develops. As a result of decreased availability of oxygen to tissues in shock, an increased demand is placed on anaerobic metabolism, leading to decreased tissue ATP levels.

Studies have shown that ATP levels in liver and kidney decrease significantly even during early shock (Table 1). In contrast to metabolically active organs, there is no decrease in skeletal muscle ATP levels during early hemorrhagic shock in conscious animals. During late shock, however, ATP levels in skeletal muscles decrease significantly. The maintenance of adenine nucleotides and creatine phosphate levels during early shock is probably due to the fact that skeletal muscles have a highly glycolytic system and low resting metabolism and are therefore able to resist the effects of reduced blood flow and hypoxia. However, skeletal muscle does require energy to maintain resting metabolism and cannot resist decreased blood flow for long periods of time as is evident in late shock.

Table 1
Effect of Shock on Tissue ATP Levels

	Liver	Kidney	Muscle
Controls	1.85 ± 0.03	1.22 ± 0.02	3.63 ± 0.23
Early shock	0.35 ± 0.04	0.36 ± 0.07	3.73 ± 0.20
Late shock	0.27 ± 0.04	0.33 ± 0.06	1.61 ± 0.10

Values are means ± SE in μmol/g tissue.

The reason for the decrease in tissue ATP levels will now be discussed. The cell normally possesses a mechanism for maintaining ATP levels. However, if the production of ATP Is slower than its utilizaton, this would result in decreased levels of the nucleotide. An oxygen deficit has been shown in the liver during shock and ischemia. A lack of oxygen causes anaerobic metabolism, which is not an efficient system for producing ATP. Whereas 36 mol ATP are synthesized from each mole of glucose during aerobic conditions, only 2 mol of ATP/mol of glucose are produced through anaerobic glycolysis. Since anaerobic metabolism in mammalian tissues is not an efficient system for providing the body's need for ATP, the ATP levels decrease under such conditions. Moreover, it is possible that the purine base for the restoration of cellular ATP is lost during shock, and thus the levels of this nucleotide cannot be restored under such conditions. In addition, a loose coupling of mitochondrial respiration or uncoupling within 1 h after the onset of severe hemorrhagic hypotension has been shown to occur, and it has been hypothesized that an uncoupled respiration may form part of the irreversible shock syndrome. Even when normal blood volume is returned, most of the derangements of the metabolic process persist in the irreversible shock state. This indicates that persistent ischemia of peripheral tissues occurs or that cells are unable to utilize oxygen even when it is available after shock. Electron microscopy and histochemical studies indicate that a number of major changes in the cell structure, including membrane-bound cytoplasmic vacuoles, loss of nucleochromatin, and leakage of endogenous pyridine nucleotides, occur in shock.

Lactate and pyruvate levels also increase in shock due to anaerobic glycolysis and decreased utilization of these compounds. Moreover, lactic acid accumulates within the cells as a result of the inability of pyruvate in the absence of adequate oxygen to pursue its normal pathways via acetyl-CoA into the tricarboxylic acid cycle. The block in the glycolytic pathway leads to a tendency of glucose to leave the cell and also results in reduced formation of ATP. This inability of cells to form sufficient amounts of ATP during low-flow conditions leads to an accumulation of phosphates within the cell and later in the blood. With the fall in energy available to the cell, one would expect its vital function to deteriorate. The critical place of ATP in carbohydrate metabolism and tissue respiration, as an energy supply of various intracellular reactions and in muscle contractions, is well recognized. Thus, with the decrease in tissue ATP levels one would expect derangements in the vital functions of the cell. The question that has not yet been answered,

Table 2

cAMP Levels During Shock

	Liver	Kidney	Muscle	Brain
Control	1,242	1,602	917	3,785
Shock receiving saline	482	638	690	2,315

Values are given in pmol/g.

however, concerns the critical levels of ATP at which aberrations or problems begin to appear in the cell membrane. Thus one does not know whether the decrease in ATP levels in metabolically active tissues during shock represents an energy crisis within the cell. If there is indeed an energy crisis within the cell, it is not known whether this occurs in the parenchymal or the endothelial cells.

Alterations in cAMP

It is well known that adenosine 3',5'-cyclic monophosphate (cAMP) regulates the control of many cellular processes. Thus inhibition of this system could result in the loss of control of many systems that contribute to homeostasis. Since the formation of cAMP is through ATP and since ATP levels in various tissues decrease during shock, it seems reasonable to expect that the cAMP levels in tissues other than liver might also be altered by prolonged blood loss. Studies have, in fact, shown that cAMP levels decrease significantly in various tissues and organs during shock (Table 2). The decreases in cAMP levels follow the same trends in various organs and tissues as the decreases in ATP levels, suggesting that those two events are related.

A question that could be raised, however, is what is the reason for the decrease of cAMP during shock and low-flow conditions. The cellular deficit in cAMP levels during shock may be due to membrane adenylate cyclase alterations, increased phosphodiesterase activity, or changes due to cellular anoxia. The other possible explanation is that the decrease in cAMP levels during shock is due to a chemical or functional deficit of the substrate ATP within the cell.

Transmembrane Potential Changes

A number of investigators have measured potential differences across the cell membrane and found that hepatic cellular membrane potential decreases progressively during shock (9). With this change in membrane potential in the liver during shock (Table 3), one would expect, according to the chloride space and Nernst equation, that sodium and water entered the cell and potassium left the cell. Studies have, in fact, demonstrated alterations in tissue sodium and water during shock. Some recent studies have reported that a linear correlation exists between the extent of the membrane potential decrease and tissue increase in lactate or decrease in pH or high-energy phosphagens. Thus it could be suggested that the decrease in transmembrane potential is directly correlated with the extent of cellular metabolic disturbance. In contrast to that in liver, the membrane potential in skeletal muscle decreases only in the late stages of shock.

Table 3

Transmembrane Potential (E_m) in Rat Liver

	mV
Control	−40.4 ± 0.4
Intermediate shock	−30.9 ± 2.0
Late shock	−18.8 ± 0.4

Values for transmembrane potential (E_m) are given in mV.

More recent studies have shown that membrane potential in liver decreases immediately after blood withdrawal, and since it is unlikely that tissue ATP levels decrease that rapidly, it could be concluded that the decrease in membrane potential is due to factors other than a decrease in tissue ATP levels.

Cell Membrane Transport

Since the potential differences across the cell membrane decrease in liver early in shock, let us examine whether the cell membrane transport process is altered. The cell membrane is freely permeable to water, but the movement of most solutes is restricted. The mechanisms for the passage of solutes across the cell membrane are diffusion, facilitated diffusion, and active transport. Diffusion is the movement of the particle from the side of the membrane where its concentration is high to the side where its concentration is low. The concentration is the same on both sides of the membrane for uncharged particles when diffusion equilibrium is reached. The active transport system maintains cell volume, restores cellular ionic composition, and appears to be important for cellular processes such as protein synthesis and mitochondrial oxidative phosphorylation. Thus any alterations in cell membrane transport process would be expected to have severe consequences on many synthetic pathways.

Much of our knowledge about the transport of ions in tissue cells comes from studies carried out in tissue slices. The capability of liver slices to support in vitro transport of sodium and potassium at 37°C with or without prior chilling of slices from animals in late as well as early shock was found to be greatly suppressed. In some such studies, the tissue slices were initially chilled to increase the sodium content and then rewarmed to determine the extrusion of accumulated sodium. In view of this, it could be argued that chilling of slices before measurement of sodium-potassium transport activity at 37°C produced further damage in the transport and/or permeability characteristics of the cell membrane. However, the differences between chilled and unchilled slices from animals at various stages of shock were not large enough to support the contention that chilling could have been a major cause for the decrease in in vitro cation transport on rewarming. Thus the available evidence indicates that cellular membrane function is disturbed during shock, as evidenced by disturbances in electrolyte transport characteristics of single cells and tissue slices (9).

In addition to electrolyte transport, the activity of the sodium-potassium ATPase has been measured, and it was found that there was a progressive increase in the activity of this enzyme with the progression of shock (Table 4). This increased activity could be due to sodium entering the cell and could thus be considered a mecha-

Table 4

Na^+-K^+ Activity in Shock

	Liver Microsomal Activity
Control	10
Early shock	20
Late shock	30

Values are given in nmol hydrogen ion produced.

nism by which cells attempt to pump out the increased sodium and to maintain potassium within the cell. However, as shown in Table 5, there was an increase in early shock, and a doubling of intracellular sodium occurred in late shock. Thus there are serious impairments in sodium-potassium transport capability or altered membrane permeability during shock. This defect can be corrected in the early stages of shock by volume replacement with blood and Ringers lactate; however, as shock continues, the depression of cell membrane transport is not rapidly corrected by volume treatment and thus persists (7). This therefore raises the question as to whether persistent depression of cell membrane transport may not be one of the limiting factors in severe and prolonged shock. Although the exact mechanism for the electrolyte changes that occur after shock are not known, such changes may be due to a reduction in the efficiency of an active ionic pump mechanism or a selective increase in the cell membrane permeability to ions, or both.

Consequences of Depressed Cell Membrane Transport Process

Having learned that the sodium-potassium transport process is altered during shock, let us examine what the potential consequences of the depressed cell membrane transport process might be. The involvement of sodium and potassium transport in the tonic regulation of the formation of cellular ATP via generation of ADP through the ATPase action of the pump has been proposed. The concept of control of respiration in liver via sodium-potassium transport is provided by the studies which showed that state 3 to state 4 transition could be seen by activation and inhibition of sodium-potassium transport in liver slices. In addition, a number of studies support the view that sodium-potassium transport at the plasma membrane controls respiratory ATP formation.

Since potassium has been implicated in the activation of glycolytic as well as gluconeogenic enzymes and since plasma potassium levels do increase in shock, these observations further indicate the metabolic significance

Table 5

Cation Content of Liver Slices from Untreated Animals During Hemorrhagic Shock

	Sodium	Potassium
Control	155.73 ± 3.85	362.58 ± 7.31
Early shock	210.80 ± 7.70	329.68 ± 7.18
Late shock	314.03 ± 21.22	308.34 ± 11.50

Values are means ± SE for intracellular sodium and potassium in meq/kg body wt.

of the sodium-potassium transport process. The metabolic role of the sodium-potassium pump in the liver is also evident from the observation that gluconeogenic substrates can hyperpolarize the hepatic cell membrane via potentiation of active sodium-potassium transport or increased potassium conductance. The importance of pump-related maintenance of high intracellular potassium is also evident from the role of potassium in protein biosynthesis. It could therefore be concluded that sodium-potassium transport may exert an indirect regulatory influence on ATP formation via control of cells' energy-consuming protein synthetic activity. Since the pump activity is adversely affected in severe shock, a number of alterations in cellular and subcellular functions would be expected to occur under those conditions.

Changes in Lung and Erythrocyte Electrolytes During Shock

Since shock produces pre- and/or postcapillary constriction, one would expect circulatory derangements in the lung that should contribute toward altered lung perfusion. Studies have, however, indicated that active sodium-potassium transport and energy levels in the lung are not affected by severe hemorrhagic shock in contrast to liver in which both are reduced (7).

There is controversy concerning whether or not there are structural changes in the lung during shock. The differences in the results may be related to fixation technique and/or are dependent on whether the lungs were inflated or deflated during fixation. It would appear, however, that the structural as well as functional energetic aspects of transmembrane sodium-potassium transport are preserved in the lung with hemorrhagic shock. However, there is a tendency for the interstitial tissue to accumulate water. Although maintenance of normal ATP in the lung and decreased ATP in the liver in hemorrhagic shock may be related to active transport in the respective organs, factors other than ATP such as structural, functional, and/or biochemical integrity of cellular membranes may be more important determinants of the transport function in the lung with shock.

A number of studies have reported that sodium levels in the erythrocyte increase significantly during hemorrhagic shock in humans. However, experimental hemorrhagic shock studies in animals indicate that even in severe hemorrhagic shock only small alterations in erythrocyte sodium-potassium levels were observed. Moreover, the results showed that large changes in erythrocyte cation levels were observed only if animals subjected to hemorrhagic shock were retransfused with acid-citrate-dextrose-preserved whole blood. Other studies have reported a direct correlation between erythrocyte sodium level and the quantity of blood transfused during the resuscitation of humans in hemorrhagic shock. Thus transfusion of stored blood with altered erythrocyte cations appears to be responsible for the large cation alterations seen in humans during shock.

Insulin Resistance During Shock

Let us now examine the issue of insulin resistance during shock. It is well known that circulatory failure produces complex neural and hormonal adjustments that result in a rapid increase in blood glucose levels. As hypovolemia continues, the progressive rise in glucose

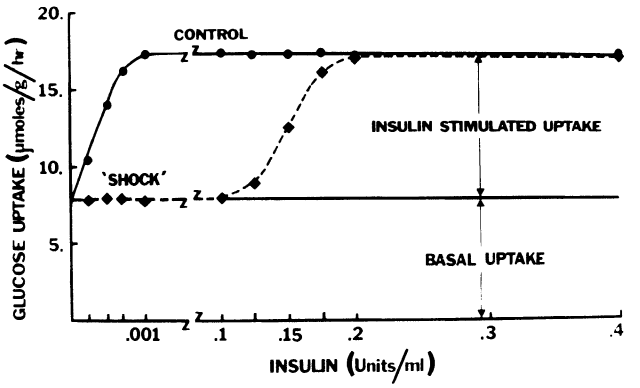


Figure 3
Insulin resistance during shock.

levels changes to a decline, at least in experimental animals in shock. This may be due to failure of gluconeogenesis. Severe injury and shock in humans are associated with hyperglycemia and an abnormality of glucose tolerance that persists after the injury. Studies have indicated that insulin levels increase during shock and that tissues' ability to respond to insulin is diminished. Moreover, the studies have indicated that hemorrhagic shock was followed by insulin resistance (Figure 3) and an abnormality of glucose and amino acid metabolism in skeletal muscle but that these abnormalities were not dependent on the concurrent changes in plasma levels of adrenal steroids or catecholamines. Recent clinical studies using a modification of the euglycemic insulin clamp technique have suggested that insulin resistance after injury occurs in skeletal muscle and is consistent with the postreceptor defect; i.e., there may be an intracellular defect in glucose metabolism after injury and trauma. Despite extensive studies, the cause or causes of insulin resistance in peripheral tissues is not known. In addition to peripheral insulin resistance, there may be insulin resistance in the liver after sepsis or trauma.

Reticuloendothelial Function

A strong relationship among the reticuloendothelial system (RES), phagocytic activity, and survival after shock has been suggested by a number of studies. It has also been shown that shock induces a state of RES depression which is directly proportional to the severity of the insult (6, 8). Moreover, it has been shown that animals which survive shock manifest only transient RES depression with subsequent recovery and that animals which eventually die as a result of shock are characterized by a persistent and progressive depression in RES function. The depression in phagocytosis that occurs in shock has been reported to be associated with humoral opsonic dysfunction (8). Although studies have suggested that hypoglycemia induces RES depression, further studies are needed to determine the cellular metabolic effects of shock and ischemia on the RES function. Moreover, additional studies are needed to determine whether the alterations in the detoxifying function of the reticuloendothelial cells are solely due to deficiencies of ATP, tuftsin or opsonins.

Effect of Lysosomes

Although lysosomes are widely distributed in a variety of tissues, the highest concentration of lysosomes is found in the liver, kidney, and spleen. It has been suggested that lysosomal enzymes are released not only from dead cells undergoing autolysis but also as a result of cellular anoxia, ischemia, and acidosis. It appears that, in the irreversible phase of shock, further deterioration of cell and organ function continues and eventually the intracellular organelles, i.e., lysosomes, begin to leak (5). These hydrolytic enzymes may then be involved in further damage inside the cell. The cell is eventually destroyed, and as this occurs, other toxic factors may be released to make this a vicious cycle affecting adjoining cells and other tissues and organs.

Progressive Cell Injury with Shock and Ischemia

From work over the years from a number of laboratories including our own, a sequence of events of progressive cell injury that occurs with insults such as shock and other forms of trauma can be proposed. The scheme of events provided in Figure 4 are based on data from animal studies and clinical observations. There is decreased blood flow initially with shock and ischemia that results in decreased oxygenation and removal of waste products. The accumulated waste products, if not cleared, will eventually depress the RES function. Fluid shifts occur as a result of neuroendocrine system activation and extracellular and intracellular matrix changes. At the cell level, the initial insult seems to occur at the cell membrane. Membrane function is altered along with permeability changes. The membrane potential decreases, sodium enters and potassium leaves the cell, lactate and hydrogen production increases within the cell, the NAD:NADH is decreased, and this in turn also alters transport processes. With increased sodium in the cell, sodium-potassium ATPase is activated, ATP is used, and the mitochondria are stimulated to increase ATP production. cAMP levels also decrease, and this may alter the effect of various hormones. Calcium regulation is compromised both at the cell membrane and the mitochondrial level, further decreases in ATP occur, and as membrane transport is depressed, more sodium enters the cell and potassium is lost.

As cell injury with decreased blood flow continues, mitochondria and endoplasmic reticulum as well as the cell tend to swell. Metabolic capabilities further decrease, and less ATP is produced because of the shift to anaerobic glycolysis from oxidative metabolism. Thus further lactic acid production occurs. Electron transport is depressed, leading to further abnormalities in mitochondrial function. The deterioration continues, and eventually the lysosomes leak and the cell is destroyed. This, then, may be the cycle of deterioration by which one cell and its products can damage adjoining cells due to release of hydrolytic enzymes. It should be pointed out that after cell swelling develops, the blood flow to tissues does not return rapidly toward normal with treatment or improvement in cardiac output. Termination of the ischemic insult may therefore not result in an immediate return of normal blood flow, distribution of nutrients, and diffusion through such swollen tissues. Thus part of the problem after the ischemic insult may be caused by continued ischemia because of parenchymal and endothelial cell swelling. Sludging of blood may also be a contributing factor. The evidence for the various events described in Figure 4 is presented in detail previously (4). These progressive and interrelated effects

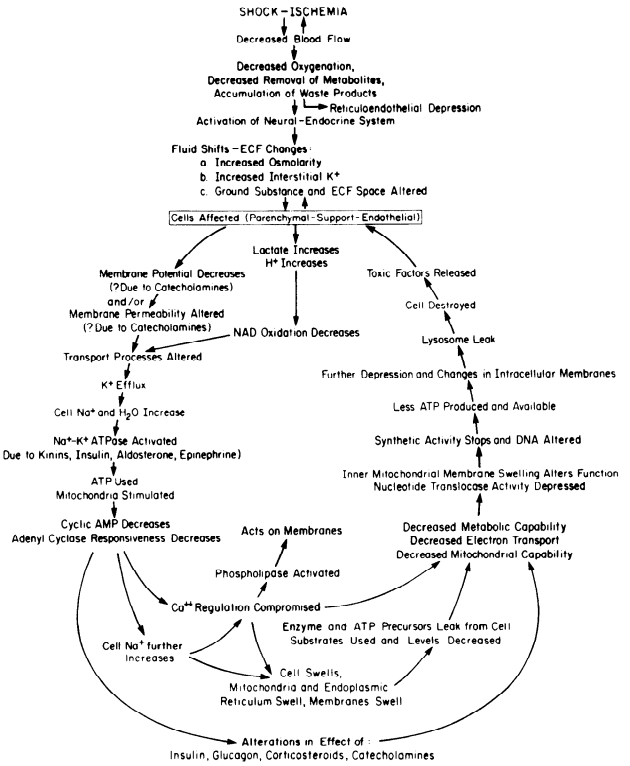


Figure 4
Cell injury with shock-ischemia.

on cell function will occur in any organ in which blood flow is decreased and will form a cycle of alterations leading to cell and organ death. The information derived from the studies listed above, however, is beginning to lead to more specific approaches to the treatment of shock.

Correction of Alterations in Cellular Abnormalities After Shock and Ischemia

The abnormalities in cell function and cell injury can usually be corrected by improving the circulation. Blood or fluids that provide and maintain an adequate vascular volume after an ischemic episode or during shock are often sufficient to correct the problem. If this regimen is not successful, then the use of inotropic agents to increase cardiac output and improve blood flow may be required. In addition to this, various adjunctive agents and approaches may be used such as buffering agents, oxygen, steroids, and other methods of circulatory support. Correction of specific alterations in cell function, however, may be necessary if the foregoing nonspecific treatment of circulation is ineffective. In view of the fact that metabolic problems and alterations in cell function occur during shock and ischemia, an exciting area of research now, and in the future, for the treatment of such conditions is that of direct correction of various metabolic problems and alterations in the above described cell function.

Pharmacological interventions that improve blood flow, the microcirculation, and cell function such as membrane transport, energy status, and electrolyte balance after shock and ischemia are necessary when volume restoration and conventional means of circulatory support have failed. Although hemodilution may decrease sludging of blood and hypertonic mannitol may help to decrease cell swelling, such manipulations do not directly improve cell metabolism and function. Attempts have been made to provide for these needs by treatment with substrates or compounds that improve energy production or supply within the cell under adverse circulatory conditions. These include the use of cAMP, creatine phosphate, allopurinol, glucose-insulin-potassium, and other substances that have been reviewed recently (3). Although provision of substrates may improve cellular energy levels, they may not necessarily improve the micro-circulation.

Other pharmacological agents including angiotensin-converting enzyme inhibitors, aprotinin, calcium channel blocking agents, coenzyme Q_{10}, fructose 1,6-diphosphate, naloxone, prostacyclin, reduced glutathione, ribose, stroma-free hemoglobin, and thromboxane inhibitors are being evaluated. Although various beneficial effects of the above agents have been reported, detailed studies of most of these agents on cellular function and microcirculatory blood flow after shock and ischemia have not been carried out adequately.

The use of ATP-$MgCl_2$ as an adjunct in the treatment of shock and ischemia will now be discussed. Whether it is a substrate, energy provider, or pharmacological agent has not been established. It has been hypothesized that ATP-$MgCl_2$ may help parenchymal cells both directly and through an improvement in microcirculation. The net result would thus be an improvement in organ blood flow and an amelioration of depressed cell function and energy metabolism after adverse circulatory conditions.

Studies from a number of laboratories have shown that infusion of ATP-$MgCl_2$ proved beneficial for the survival of animals after hemorrhagic shock, severe burns, sepsis-peritonitis, postischemic hepatic failure, and endotoxic shock (2). Moreover, ATP-$MgCl_2$ has been shown to accelerate the recovery of renal function after acute renal failure in difference species of animals. In addition, it has been shown that kidneys that were subjected to episodes of warm ischemia could be salvaged by addition of ATP-$MgCl_2$ to the perfusate. ATP-$MgCl_2$ has also been effective in hastening renal recovery from a toxic injury (2). It has also been shown that pretreatment of mice with ATP before subjecting them to global hypoxia produced an increased survival time of 794% over that of mice treatment with saline. In addition, ATP-$MgCl_2$ is being used clinically in Japan for the treatment of acute renal failure and other adverse circulatory conditions and the reported results are very encouraging. The hazards, controversies, and precautions in using ATP-$MgCl_2$ are provided in detail in a recent publication (4). The issue that should be discussed, however, is whether infused ATP-$MgCl_2$ corrects the abnormalities in cell function after shock or ischemia.

Studies have shown that ATP-$MgCl_2$ administration following shock or ischemia improves total blood flow and microcirculatory blood flow and restores RES function and immunocompetence. ATP-$MgCl_2$ also improves metabolic capacity, improves cell function, and corrects hormonal imbalance following shock or ischemia. The effects of ATP-$MgCl_2$ after shock or ischemia that have been well-documented or for which there is some experimental evidence are listed in Figure 5 (2).

Provision of energy (ATP) that does not have to pass through the glycolytic pathway, the tricarboxylic acid cycle, and the electron transport chain to produce ATP

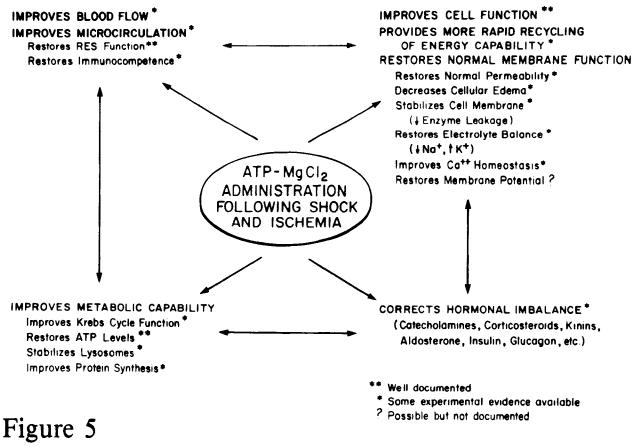


Figure 5
Effects of ATP-$MgCl_2$ following shock-ischemia.

therefore appears to be a direct and advantageous method for the treatment of shock and ischemia when fluid and vasoactive agents are not effective. In this regard, studies have shown that ATP can cross the cell plasma membrane as ATP (2). Alternatively, the effects of ATP-$MgCl_2$ may not be to provide a large amount of energy in itself but, rather, to catalyze improvement of energy production or improvement in the microcirculation through extracellular effects mediated by cell surface ATP receptors or phosphorylation of membrane proteins. The mechanism by which these effects are exerted, however, is unclear and thus requires further study.

References

1. Altura, B. M. Endothelium, reticuloendothelial cells, and microvascular integrity: roles in host defense. In: *Handbook of Shock and Trauma*, edited by B. M. Altura, A. M. Lefer, and W. Schumer. New York: Raven, 1983, vol. 1, pp. 29–49.
2. Chaudry, I. H. Cellular mechanisms in shock and ischemia and their correction. *Am. J. Physiol.* 245 (*Regulatory Integrative Comp.* 14): R117–R134, 1983.
3. Chaudry, I. H., and A. E. Baue. Overview of hemorrhagic shock. In: *Pathophysiology of Shock, Anoxia and Hypoxia*, edited by R. A. Cowley, and B. F. Trump. Baltimore, MD: Williams & Wilkins, 1982, pp. 203–219.
4. Chaudry, I. H., M. G. Clemens, and E. A. Baue. Alterations in cell function with ischemia and shock and their correction. *Arch. Surg.* 116: 1309–1317, 1981.
5. Lefer, A. M. Properties of a cardio-inhibitory factor produced in shock. *Federation Proc.* 37: 2734–2740, 1978.
6. Nagler, A. L., and R. McConn. The role of humoral factors in shock. In: *Shock: Clinical and Experimental Aspects*, edited by I. M. Ledingham. Amsterdam: Excerpta Med., 1976, pp. 76–109.
7. Mela, L. Mitochondrial function in shock, ischemia and hypoxia. In: *Pathophysiology of Shock, Anoxia and Ischemia*, edited by R. A. Cowley, and B. F. Trump. Baltimore, MD: Williams & Wilkins, 1982, pp. 6–46.
8. Saba, T. M., and E. Jaffee. Plasma fibronectin (opsonic glycoprotein): its synthesis by vascular endothelial cells and role in cardiopulmonary integrity after trauma as related to reticuloendothelial function. *Am. J. Med.* 68: 577–594, 1980.
9. Sayeed, M. M. Membrane Na^+-K^+ transport and ancillary phenomenon in circulatory shock. In: *Pathophysiology of Shock, Anoxia and Ischemia*, edited by R. A. Cowley, and B. F. Trump. Baltimore, MD: Williams & Wilkins, 1982, pp. 112–132.
10. Siegel, J. H., F. B. Cerra, J. R. Border, B. Coleman, and R. H. McMenamy. Human responses to sepsis: a physiologic manifestation of disordered metabolic control. In: *Pathophysiology of Shock, Anoxia and Ischemia*, edited by R. A. Cowley, and B. F. Trump. Baltimore, MD: Williams & Wilkins, 1982, pp. 235–253.

Shock and Ischemia Multiple Choice Questions

1. Which of the following statements concerning acute loss of circulating blood volume is incorrect?
   a. it initiates an intense neurohormonal activation
   b. it initiates the release of various vasoactive agents
   c. it produces hemodynamic disturbances
   d. without tissue trauma it does not initiate neurohormonal activation
   e. it produces alterations in cell function

2. Which of the following conditions produces an abnormality in mitochondrial function?
   a. a lack of oxygen
   b. defects in electron transport-linked carriers
   c. defects in electron transport-linked enzymes
   d. lack of substrates such as succinate or α-ketoglutarate
   e. a defect or deficiency in any of the above

3. Mitochondrial metabolism in shock is more adversely affected with α-ketoglutarate in comparison to succinate. The reason for this is:
   a. mitochondria preferentially use succinate during shock
   b. α-ketoglutarate has higher affinity for mitochondria
   c. succinate enters directly into tricarboxylic acid cycle without involving NAD and coenzyme A
   d. succinate is not needed for ATP formation
   e. succinate is preferentially used in the cytoplasma

4. Mitochondrial function is depressed during shock. The depression in mitochondrial function during shock may be due to:
   a. ultrastructural changes in mitochondria
   b. loss or leakage of various cofactors from the mitochondria
   c. decreased redox potential
   d. altered cations or elevated free fatty acids in the mitochondria
   e. any or all of the above

5. What percent of the cell's energy requirements are provided by the mitochondria?
   a. a negligible amount
   b. 25%
   c. 50%
   d. 75%
   e. 95%

6. Intact hepatic mitochondrial function prevents lactic-acidosis because:
   a. mitochondrial enzymes convert lactate to malate
   b. lactate is absorbed by proteins in the mitochondrial membrane
   c. reducing equivalents are transferred there for complete oxidation of lactate to pyruvate
   d. mitochondria help maintain an alkaline intracellular pH
   e. the statement is false

7. Tissue ATP levels decrease during shock. The reason for this is:
   a. there is an oxygen deficit
   b. anaerobic metabolism is less effective than aerobic metabolism
   c. substrate supply is decreased
   d. mitochondrial function is decreased
   e. any or all of the above

8. In which of the following organs or tissues would ATP levels be expected to decrease during the early stages of shock?
   a. brain
   b. myocardium
   c. skeletal muscle
   d. liver
   e. skin

9. During severe shock, there are various alterations in cell and organ function. Which of the following statements is incorrect?
   a. there is depression in reticuloendothelial function
   b. interstitial potassium is decreased
   c. there is insulin resistance
   d. cell membrane transport processes are severely impaired
   e. there is lysosomal breakdown

10. Administration of ATP-$MgCl_2$ as an adjunct following shock and ischemia improves various cellular functions and survival of the animals. ATP-$MgCl_2$ produces these effects by:
   a. improving microcirculatory and total blood flow
   b. improving cell functions
   c. improving metabolic capability
   d. correcting hormonal imbalance
   e. all of the above

ANSWER FORM FOR CME TEST CREDITS

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Acid-Base Disorders — A Computer Simulation

DAVID L. MAUDE
Department of Physiology
New York Medical College
Valhalla, New York 10595

The wide use of arterial blood gas analysis in clinical medicine has made it increasingly important for physicians to understand the behavior of the bicarbonate-carbon dioxide buffer system in acid-base disorders. The medical school course in Physiology is generally their first exposure to this arcane subject. To familiarize our students with the arterial blood gas parameters and their responses to changes in hydrogen ion (H^+) balance, we conduct a laboratory in which acute metabolic and respiratory acid-base disorders are produced in anesthetized dogs. The procedures to which the animals are being subjected are unknown to the students, who obtain arterial blood samples and follow the changes in pH, carbon dioxide partial pressure (P_{CO_2}), and bicarbonate ion concentration ($[HCO_3^-]$) over a period of several hours. Using this data they attempt to arrive at an acid-base diagnosis. The laboratory is generally successful in exciting interest in acid-base physiology and in creating familiarity with the blood gas parameters and the ways in which they change when the H^+ equilibrium is disturbed.

Expense and the constraints of time limit the amount of data that can be generated by this laboratory. We now supplement it with a computer simulation which prompts the student to disturb the acid-base status of a hypothetical patient by "infusing" a chosen quantity of acid or alkali or altering the alveolar P_{CO_2}. The program calculates the resulting changes in arterial pH, $[HCO_3^-]$, and the titration of fixed body buffers. A post-compensation pH or $[HCO_3^-]$ lying outside the limits defined for simple normally compensated disorders will be commented on. A typical run produced the display shown in Figure 1.

The rationale for the program is as follows. The initial responses of arterial pH and $[HCO_3^-]$ to the addition or removal of H^+ or to changes in P_{CO_2} are governed by the capacities and pK of the body buffer systems. These parameters also determine the shape of the CO_2 titration curve or whole-body buffer line, which is generated from data obtained in acute CO_2 breathing and hyperventilation experiments on normal human subjects. The CO_2 titration curve is often drawn to show the relationship between changes in arterial pH and $[HCO_3^-]$ on the familiar pH-bicarbonate diagram (Figure 2). The function is more conveniently expressed mathematically as an empirical equation relating $[HCO_3^-]$ to P_{CO_2}

$$[HCO_3^-] = S * P_{CO_2}/(P_{CO_2} + R) \qquad (1)$$

where the coefficients R and S have values of 12.95 mmHg and 31.39 meq/l, respectively (8). *Equation 1* is used directly to calculate the $[HCO_3^-]$, and hence the pH, in acute respiratory acidosis and alkalosis. Since the quantity of HCO_3^- generated when CO_2 reacts with non-bicarbonate body buffers (B^-, HB) is equal to the amount of fixed buffer titrated ($CO_2 + H_2O + B^- <----> HB$

```
WHICH ACID-BASE DISORDER DO YOU WISH TO STUDY?

METABOLIC ACIDOSIS?  THEN TYPE "A"
METABOLIC ALKALOSIS? THEN TYPE "L"
RESPIRATORY ACIDOSIS? THEN TYPE "R"
RESPIRATORY ALKALOSIS (HYPERVENTILATION)? THEN TYPE "H"

  ( PRESS (RETURN) AFTER KEYBOARD ENTRY.)

A

ENTER PT"S BODY WEIGHT IN KG.   70.0

ENTER MEQ. ACID ADDED. (TO CAUSE A SIGNIFICANT pH DISTURBANCE
THE AMOUNT ADDED MUST EXCEED 0.5 mEq/Kg BODY WT.)   250.0

BEFOR RESPIRATORY COMPENSATION (PCO2 =  40.0):

    PH =  7.19.  HCO3 =  14.7 MEQ/L.

OF  250.0 MEQ ACID ADDED  140.0 HAVE REACTED
WITH FIXED BODY BUFFERS.

ENTER A VALUE (<40 MMHG) FOR PCO2 DURING RESP. COMPENSATION.   34.0

AFTER RESPIRATORY COMPENSATION TO PCO2 =  34.0 :

PH =  7.25   HCO3 =  14.3 MEQ/L

 84.0 MEQ H+ IONS REMAIN ON FIXED BODY BUFFERS.

  NOTE: A PCO2 OF  34.0 IS HIGHER THAN EXPECTED DURING RESPIRATORY COMPENSATION
FOR THIS DEGREE OF ACIDOSIS. YOU SHOULD SUSPECT A DISTURBANCE IN PULMONARY
VENTILATION OR ITS CONTROL.

DO YOU WANT TO RUN THE PROGRAM AGAIN? Y(es)/N(o)

  ( PRESS (RETURN) AFTER KEYBOARD ENTRY.)
```

Figure 1
Typical display generated during a single run of the program (user responses underlined).

+ HCO_3^-), *Eq. 1* can also be the basis for calculating the extent of buffering as well as the final pH and $[HCO_3^-]$ in a metabolic acid-base disturbance. In an uncompensated metabolic acidosis, for example, the amount of B^- titrated to HB equals the increase in body bicarbonate content that would occur during a CO_2 titration to the same pH (the equivalent CO_2 titration) (see Figure 2). The increase in bicarbonate content is the product of the bicarbonate space (V) and the change in $[HCO_3^-]$ from its normal value (here taken as 23.7 meq/l), as calculated from *Eq. 1*. V is the true volume of distribution of HCO_3^- *not* the apparent bicarbonate space derived from studies where $NaHCO_3$ is infused into acidotic patients or experimental animals. The latter volume, typically taken as 0.5 l/kg body wt (12) or more in severe acidosis (9), exceeds the actual bicarbonate space because some of the infused bicarbonate reacts with protonated body buffers (HB) and is excreted via the lungs as CO_2

$$HCO_3^- + HB \text{ ----> } B^- + CO_2 + H_2O$$

V cannot be measured but in view of the negative electrical potential and relatively low pH [about 7.0 (11, 18)] prevailing within most of the body's cells is unlikely to include any significant amount of intracellular fluid. We have therefore taken V to be the same as the extracellular fluid volume, i.e., 0.2 l/kg body wt.

Description of the Program

The program as listed in Figure 3 was written for the Apple Pascal Version 1.1 operating system. With minor modifications it could be adapted to run with other Pascal compilers. Its key components are as follows.

1. The functions PCO2TCAL and HCO3TCAL, which use *Eq. 1* to calculate the P_{CO_2} and $[HCO_3^-]$ (PCO2T, HCO3T) in an equivalent CO_2 titration.
2. The functions PHHH and HCO3HH, which calculate pH and $[HCO_3^-]$ using the Henderson-Hasselbalch equation.
3. The procedure MET, which calculates the contributions of the bicarbonate and nonbicarbonate buffer systems to the buffering of an acid or alkali load. When applied to a metabolic acidosis (in the procedure METACID), MET iteratively increases HCO3T from an initial value of 23.7 meq/l (HCO3N) and calculates the corresponding P_{CO_2} and pH (PCO2T,

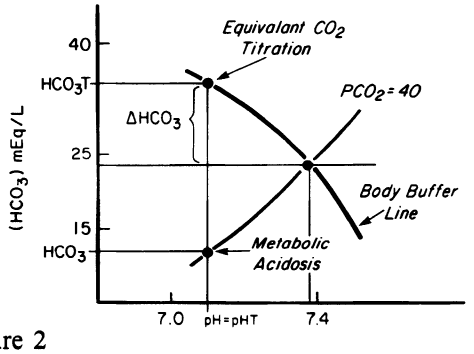

Figure 2
pH-bicarbonate diagram showing points for an uncompensated metabolic acidosis and its equivalent CO_2 titration. Increase in bicarbonate concentration (ΔHCO_3) in the equivalent titration is used to calculate the quantity of H^+ reacting with fixed buffers during the corresponding metabolic acidosis.

Figure 3
Program listing

Program listing 1

```
PROGRAM PHCHANGE;
    USES TRANSCEND;
    CONST
      V=0.2;(*TRUE HCO3 SPACE - L/KG*)
      HCO3N=23.7;PCO2N=40;PHN=7.40;(*NORMAL VALUES*)
      S1=' ( PRESS <RETURN> AFTER KEYBOARD ENTRY.)';
    VAR
      R(*PCO2 CONST*), S(*HCO3 CONST.*),
      W(*BODY WT*),BTR,(*BUFFER TITRATED IN RESP. DISORDER*)
      LOAD(*MEQ ACID/BASE ADDED*),A(*LOAD/KG*),
      PH,PHT,PCO2,PCO2T,HCO3,HCO3T, DELTA, FRACTION: REAL;
      CHOICE, OPTION:CHAR;
    FUNCTION PHHH(HCO3,PCO2:REAL):REAL;
      BEGIN
        PHHH:=7.62+LOG(HCO3/PCO2)
      END;(*PH CALC FROM HEND.-HAS. EQ.*)
    FUNCTION PCO2TCAL(R,S,HCO3T:REAL):REAL;
      BEGIN
        PCO2TCAL:=R*(HCO3T/(S-HCO3T))
      END;(*PCO2 FROM NORMAL BUFFER EQ.*)
    FUNCTION HCO3TCAL(R,S,PCO2T:REAL):REAL;
      BEGIN
        HCO3TCAL:=S*PCO2T/(R+PCO2T)
      END;(*HCO3 FROM NORMAL BUFFER EQ.*)
    FUNCTION HCO3HH(PH,PCO2:REAL):REAL;
      BEGIN
        HCO3HH:=PCO2*EXP(2.303*(PH-7.62))
      END;(*HCO3 FROM HEND.-HAS. EQ.*)
    FUNCTION HCAL(R:REAL):REAL;
      BEGIN
        HCAL:=R*HCO3N/PCO2N + HCO3N
      END;(*CALCULATE S FROM R*)
PROCEDURE GETWT;
   BEGIN
     WRITE('ENTER PT'S BODY WEIGHT IN KG.  ');
     READLN(W);
   END;(*GETWT*)
PROCEDURE MET;
   BEGIN
     REPEAT
       PCO2T:=PCO2TCAL(R,S,HCO3T);
       PHT:=PHHH(HCO3T,PCO2T);
       HCO3:=HCO3HH(PHT,PCO2);
       HCO3T:=HCO3T+FRACTION*DELTA;
     UNTIL DELTA*(HCO3T-HCO3)>=A/V;
   END;(*MET*)
PROCEDURE RESPCOMP;
   BEGIN
     REPEAT
       PH:=PHHH(HCO3,PCO2);
       PCO2T:=PCO2TCAL(R,S,HCO3T);
       PHT:=PHHH(HCO3T,PCO2T);
       HCO3T:=HCO3T-FRACTION*DELTA;
       HCO3:=HCO3-0.1*DELTA;
     UNTIL (PH-PHT)*DELTA <= 0.01;
   END;(*RESPCOMP*)
```

Program listing 2

```
PROCEDURE MACLIMITS;
   BEGIN
     IF PCO2>(1.54*HCO3+10.56) THEN
       BEGIN
         WRITELN('  NOTE: A PCO2 OF ',PCO2:3:1,' IS HIGHER THAN EXPECTED');
         WRITELN('DURING RESPIRATORY COMPENSATION FOR THIS DEGREE OF ACIDOSIS.');
         WRITELN('YOU SHOULD SUSPECT A DISTURBANCE IN PULMONARY VENTILATION OR');
         WRITELN(' ITS CONTROL.');
       END;
     IF PCO2<(1.54*HCO3+6.16) THEN
       BEGIN
         WRITELN('  NOTE: A PCO2 OF ',PCO2:3:1,' IS LOWER THAN EXPECTED DURING');
         WRITELN(' RESPIRATORY COMPENSATION FOR THIS DEGREE OF ACIDOSIS.  YOU ');
         WRITELN('SHOULD SUSPECT THAT THE PATIENT HAS A COMBINED METABOLIC ');
         WRITELN('ACIDOSIS AND A PRIMARY RESPIRATORY ALKALOSIS.');
       END;
   END;(*MACLIMITS*)
PROCEDURE MALLIMITS;
   BEGIN
     IF PCO2>0.91*HCO3+20.7 THEN
       BEGIN
         WRITELN('NOTE: A PCO2 OF ',PCO2:3:1,' IS HIGHER THAN EXPECTED DURING ');
         WRITELN('RESPIRATORY COMPENSATION FOR THIS DEGREE OF ALKALOSIS.  YOU ');
         WRITELN('SHOULD SUSPECT THAT THE PATIENT HAS A PRIMARY RESPIRATORY ');
         WRITELN('ACIDOSIS IN ADDITION TO THE METABOLIC ALKALOSIS.');
       END;
     IF PCO2<(0.91*HCO3+10.5 THEN
       BEGIN
         WRITELN('  NOTE: A PCO2 OF ',PCO2:3:1,' IS LOWER THAN EXPECTED DURING ');
         WRITELN('RESPIRATORY COMPENSATION FOR THIS DEGREE OF ALKALOSIS.  YOU ');
         WRITELN('SHOULD SUSPECT THAT THE PATIENT HAS A PRIMARY RESPIRATORY ');
         WRITELN('ALKALOSIS IN ADDITION TO THE METABOLIC ALKALOSIS.');
       END;
     END;(*MALLIMITS*)
PROCEDURE RACLIMITS;
   BEGIN
     IF PHT>9-LOG(0.24*PCO2+21.2) THEN
       BEGIN
         WRITELN('NOTE: A PH OF ',PHT:3:1,' IS GREATER THAN EXPECTED WITH THIS');
         WRITELN(' DEGREE OF CO2 RETENTION.  YOU SHOULD SUSPECT THAT THE ');
         WRITELN('PATIENT HAS A COMBINED RESPIRATORY ACIDOSIS AND A PRIMARY ');
         WRITELN('METABOLIC ALKALOSIS.');
       END;
     IF PHT<(9-LOG(0.24*PCO2+33.2) THEN
       BEGIN
         WRITELN(' NOTE: A PH OF ',PHT:3:1,' IS LESS THAN EXPECTED WITH ');
         WRITELN('THIS DEGREE OF CO2 RETENTION.  YOU SHOULD SUSPECT THAT THE ');
         WRITELN('RESPIRATORY ACIDOSIS IS COMBINED WITH A PRIMARY METABOLIC ');
         WRITELN('ACIDOSIS.');
       END;
   END;(*RACLIMITS*)
```

Program listing 3

```
PROCEDURE RALLIMITS;
   BEGIN
     IF PHT>9-LOG(0.74*PCO2+6.9) THEN
       BEGIN
       WRITELN
       ('NOTE:  A PH OF ',PHT:3:2,' IS GREATER THAN EXPECTED IN A PATIENT ');
       WRITELN('WITH THIS DEGREE OF HYPERVENTILATION.  YOU SHOULD SUSPECT A ');
       WRITELN('CO-EXISTING METABOLIC ALKALOSIS.');
     END;
   IF PHT<(9-LOG(0.74*PCO2+13.9) THEN
     BEGIN
       WRITELN('NOTE:  A PH OF ',PHT:3:2,' IS LESS THAN EXPECTED IN A PATIENT ');
       WRITELN('WITH THIS DEGREE OF HYPERVENTILATION.  YOU SHOULD SUSPECT A ');
       WRITELN('CO-EXISTING METABOLIC ACIDOSIS.');
     END;
  END;(*RALLIMITS*)
PROCEDURE METACID;
   BEGIN (*METABOLIC ACIDOSIS *)
     R := 40 ;  S:=HCAL(R);
     WRITELN;
     GETWT;
     WRITE('ENTER MEQ. ACID ADDED.  ');
     READLN(LOAD); WRITE(CHR(12));
     A:= LOAD/W;
     WHILE A/V)45 DO
       BEGIN
         WRITELN(LOAD:4:1,  MEQ H+ IONS CAUSED A FATAL ACIDOSIS. );
         WRITE('ENTER A NEW VALUE FOR ACID ADDED. );
         READLN(LOAD);
         A:=LOAD/W;
       END;
     PH:=PHN; PCO2:=PCO2N; HCO3T:=HCO3N; DELTA:=1;
     MET;
     WRITELN('BEFOR RESPIRATORY COMPENSATION (PCO2 = ',PCO2:3:1,'):');
     WRITELN('    PH = ',PHT:3:2,'.  HCO3 = ',HCO3:3:1,' MEQ/L.');
     WRITELN;
     WRITELN
     ('OF ',LOAD:4:1,' MEQ ACID ADDED ',(HCO3T-HCO3N)*V*W:4:1,' HAVE REACTED');
     WRITELN('WITH FIXED BODY BUFFERS.');  WRITELN;
   END;(*METACID*)
PROCEDURE MACCOMP;
   BEGIN
     WRITELN;
     WRITE
     ('ENTER A VALUE ((40 MMHG) FOR PCO2 DURING RESP. COMPENSATION.  ',S1);
     READLN(PCO2);
     WRITELN;
     RESPCOMP;
     LOAD:=(HCO3T-HCO3N)*V*W;
     WRITELN('AFTER RESPIRATORY COMPENSATION TO PCO2 = ',PCO2:3:1,' :');
     WRITELN('PH = ',PH:3:2,'   HCO3 = ',HCO3:3:1,' MEQ/L');
     WRITELN(LOAD:4:1,' MEQ H+ IONS REMAIN ON FIXED BODY BUFFERS.');
     WRITELN;
     MACLIMITS;
   END;(*MACCOMP*)

PROCEDURE METALK;
   BEGIN
     R := 12.95; S:=HCAL(R);
     WRITELN;
     GETWT;
     WRITE('ENTER MEQ. OF BASE ADDED.  ');READLN(LOAD); WRITE(CHR(12));
     A:= LOAD/W; PCO2:=PCO2N; HCO3T:=HCO3N; DELTA:=-1.0;
     MET;
     WRITELN('BEFOR RESPIRATORY COMPENSATION (PCO2 = ',PCO2:3:1,'):');
     WRITELN('PH = ',PHT:3:2,'.  HCO3 = ',HCO3:3:1,' MEQ/L.');
     WRITELN
('OF ',LOAD:4:1,' MEQ BASE ADDED ',(HCO3N-HCO3T)*V*W:4:1,' HAVE REACTED');
     WRITELN('WITH FIXED BODY BUFFERS.');WRITELN;WRITELN;WRITELN;
     WRITE
  ('ENTER A VALUE () 45 MMHG) FOR PCO2 DURING RESPIRATORY COMPENSATION.  ',S1);
     READLN(PCO2); WRITELN;
     FRACTION:=0.1;
     RESPCOMP;
     LOAD:=(HCO3N-HCO3T)*V*W;
     WRITELN('AFTER RESPIRATORY COMPENSATION TO PCO2 = ',PCO2:3:1,':');
     WRITELN('PH = ',PH:3:2,'.  HCO3 = ',HCO3:3:1,' MEQ/L.');
     WRITELN(LOAD:4:1,' MEQ OH- IONS REMAIN ON FIXED BODY BUFFERS.');
     WRITELN;
     MALLIMITS;
   END;(*METALK*)
PROCEDURE RESPACID;
   BEGIN
     R := 12.95; S:=HCAL(R);
     WRITELN;
     GETWT;
     WRITE('CHOOSE A VALUE ()40 & (100) FOR PCO2.'); READLN(PCO2);
     WRITE(CHR(12));
     HCO3:=HCO3TCAL(R,S,PCO2);
     PH:=PHHH(HCO3,PCO2);
     BTR:=(HCO3-HCO3N)*V*W;
     WRITELN('RESPIRATORY ACIDOSIS WITHOUT RENAL COMPENSATION:');
     WRITELN('PCO2 = ',PCO2:3:1,'   PH = ',PH:3:2,'  (HCO3) = ',HCO3:3:1);
     WRITELN;
     WRITELN(BTR:3:1,' MEQ. BODY BUFFER HAS BEEN TITRATED BY CO2.');
     WRITELN;WRITELN;
     WRITELN('HOW MANY MEQ OF HCO3 IONS WOULD YOU LIKE THE PATIENT'S ');
     WRITELN('KIDNEYS TO PRODUCE TO COMPENSATE FOR THE RETAINED ACID?');
     WRITE(S1);
     READLN(LOAD);
     A:= LOAD/W; HCO3T:= HCO3; DELTA:= -1.0; FRACTION:=0.2;
     MET;
     BTR:=(HCO3T-HCO3N)*V*W;
     WRITELN;
     WRITELN('AFTER RENAL COMPENSATION - PRODUCTION OF ',LOAD:3:1,' MEQ');
     WRITELN('HCO3 IONS -  PH = ',PHT:3:2,'  HCO3 = ',HCO3:3:1,' MEQ/L.');
     WRITELN;
     WRITELN(BTR:4:1,' MEQ OF FIXED BODY BUFFERS REMAIN');
     WRITELN('TITRATED WITH CO2.');
     RACLIMITS;
  END;(*RESPACID*)
```

Program listing 5

```
  PROCEDURE RESPALK;
     BEGIN
       R := 12.95; S:=HCAL(R);
       WRITELN;
       GETWT;
       WRITE('CHOOSE A VALUE ()10 & (40) FOR PCO2.  ');
       READLN(PCO2); WRITE(CHR(12));
       HCO3:=HCO3TCAL(R,S,PCO2);
       PH:=PHHH(HCO3,PCO2);
       BTR:=(HCO3N-HCO3)*V*W;
       WRITELN('RESPIRATORY ALKALOSIS WITHOUT RENAL COMPENSATION:');
       WRITELN;
       WRITELN('PCO2 = ',PCO2:3:1,'   PH = ',PH:3:2,'   (HCO3) = ',HCO3:3:1);
       WRITELN;
       WRITELN(BTR:3:1,' MEQ H+ IONS HAVE BEEN RELEASED');
       WRITELN('FROM FIXED BODY BUFFERS.');
       WRITELN;WRITELN;
       WRITELN('HOW MANY MEQ OF HCO3 IONS WOULD YOU LIKE THE PATIENT"S');
       WRITELN('KIDNEYS TO EXCRETE TO COMPENSATE FOR THE LOST CO2 ?');
       WRITE(S1);
       READLN(LOAD); A:=LOAD/W; HCO3T:= HCO3; DELTA:=1.0;
       WRITELN;
       MET;
       BTR:=(HCO3N-HCO3T)*V*W;
       WRITELN('AFTER RENAL COMPENSATION - EXCRETION OF ',LOAD:3:1,' MEQ');
       WRITELN('OF HCO3 IONS - PH = ',PHT:3:2,'  HCO3 = '.HCO3:3:1,' MEQ/L');
       WRITELN;
       WRITELN('H+ ION RELEASE FROM FIXED BODY BUFFERS IS NOW ');
       WRITELN(BTR:3:1,' MEQ.');WRITELN;
       RALLIMITS;
     END;(*RESPALK*)

(*************************************************************)

BEGIN(*PROGRAM*)
   OPTION:='Y';
   FRACTION:=1;
REPEAT
   WRITELN('WHICH ACID-BASE DISORDER DO YOU WISH TO STUDY?');
   WRITELN('METABOLIC ACIDOSIS?  THEN TYPE "A"');
   WRITELN('METABOLIC ALKALOSIS? THEN TYPE "L"');
   WRITELN('RESPIRATORY ACIDOSIS? THEN TYPE "R"');
   WRITELN('RESPIRATORY ALKALOSIS (HYPERVENTILATION)? THEN TYPE "H"');
   WRITELN;WRITELN(S1);WRITELN;
   READLN(CHOICE);WRITELN;
     CASE CHOICE OF
     'A': BEGIN METACID; MACCOMP; END;
     'L': METALK;
     'R': RESPACID;
     'H': RESPALK;
     END;(*CASE*)
   IF (CHOICE<>'A') AND (CHOICE<>'L') AND (CHOICE<>'R') AND (CHOICE<>'H')
   THEN WRITE('INCORRECT ENTRY.' );WRITELN;
   WRITELN('DO YOU WANT TO RUN THE PROGRAM AGAIN? Y(es)/N(o)');
   WRITELN;WRITELN(S1);WRITELN;
   READLN(OPTION); WRITE(CHR(12));
UNTIL OPTION<>'Y';
END.(*PROGRAM*)
```

PHT). PHT, in turn, is used to calculate [HCO_3^-] at P_{CO_2} = 40 mmHg (HCO3). Iteration continues until V*(HCO3T − HCO3) = A, the acid load/kg body wt. At this point all of the added acid has been accommodated by the body buffers and the displacements of HCO3 and HCO3T from HCO3N can be used to calculate the separate contributions of the bicarbonate and fixed buffer systems.

When Met is used to calculate the buffering of added alkali, in the procedure METALK, the sign (DELTA) of the incrementing operator is set to −1.0 and iteration continues until V*(HCO3 − HCO3T) = A, where A is now the alkali load.

MET is also used in the RESPACID and RESPALK procedures to calculate the effects compensatory renal production or excretion of bicarbonate.

4. The procedure RESPCOMP, which calculates the changes in the system variables after compensatory alterations in P_{CO_2}. When used in METACID, RESPCOMP progressively decreases both HCO3 and HCO3T and calculates new values for PH, PHT, and PCO2T. The iteration continues until PH and PHT differ by <0.01 pH unit. The values of HCO3T and PCO2T then correspond to a new equivalent CO_2 titration, from which bicarbonate and nonbicarbonate buffering can again be calculated.

Four additional procedures, MACLIMITS, MALLIMITS, RACLIMITS, and RALLIMITS, compare values of pH, P_{CO_2}, and [HCO_3^-] after student-selected compensatory responses with the expected values for normally compensated uncomplicated acid-base disorders (1, 2, 4, 5, 17). If, for example, the value of P_{CO_2} chosen by the student to compensate for a metabolic acidosis were inappropriately high, MACLIMITS would indicate this fact and suggest the possibility of a mixed acid-base disorder (see Figure 1).

In developing this program we found that the functions PCO2TCAL and HCO3TCAL accurately predict the pH and bicarbonate observed clinically during acute respiratory acid-base disorders (2, 4) as well as the ~30% nonbicarbonate buffering of acutely infused alkali (15), when *R* and *S* take on the values defined during CO_2 titration and hyperventilation experiments. In metabolic acidosis, however, nonbicarbonate buffering is underestimated. The program calculates the ~50% nonbicarbonate buffering that occurs during acute acid infusions (14, 16) only when larger values, e.g., 40 and 47, are assigned to *R* and *S*. Apparently, buffers readily assessible to infused H^+ remain untitrated during the brief duration of CO_2 titration experiments.

Several programs already published deal with acid-base imbalance (3, 6, 10, 19). Most were devised to yield an acid-base diagnosis from arterial blood gas values and prompt the user to enter various items of clinical and laboratory data the nature and significance of which may be obscure to the beginning medical student. Although these programs have heuristic value, their primary aim is to assist in patient management rather than to teach the preclinical medical student. Rasch (13) has devised a microprocessor simulation of acid-base regulation that does allow the user to test responses to acid or alkali. The input, however, is not a quantity of H^+ or OH^- but, rather, a change in the plasma concentration of acid anions or alkali cations. Reactions of the body buffers are not considered. The present model comes closer to being an acid-base simulator, for it allows the student to examine the body's responses both to primary pH-disturbing influences and to compensatory adjustments in renal or respiratory function.

The program has proven easy to use, and our students, after reading a brief descriptive paragraph that includes suggestions for "experiments" to be performed, run it without difficulty. We feel that it encourages them to think about acid-base physiology and serves as a catalyst for discussions both among the students and between students and their instructors.

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References

1. Albert, M. S., R. B. Dell, and R. W. Winter. Quantitative displacement of acid-base equilibrium in metabolic acidosis. *Ann. Int. Med.* 66: 312–322, 1967.

2. Arbus, G. S., L. E. Hebert, P. R. Levesque, B. E. Etstein, and W. B. Schwartz. Characterization and clinical application of the "significance band" for acute respiratory alkalosis. *N. Engl. J. Med.* 280: 117–123, 1969.

3. Bleich, H. L. Computer-based consultation. Electrolyte and acid-base disorders. *Am. J. Med.* 53: 285–291, 1972.

4. Brackett, N. C., Jr., J. J. Cohen, and W. B. Schwartz. Carbon dioxide titration curve of normal man. Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. *N. Engl. J. Med.* 272: 6–12, 1965.

5. Brackett, N. C., Jr., C. F. Wingo, O. Muren, and J. T. Solano. Acid-base response to chronic hypercapnia in man. *N. Engl. J. Med.* 280: 124–130, 1969.

6. Cohen, M. L. A computer program for the interpretation of blood-gas analysis. *Comput. Biomed. Res.* 2: 549–557, 1969.

7. Cooper, J. W. *Introduction to Pascal for Scientists.* New York: Wiley, 1981, p. 2.

8. Davenport, H. W. *The ABC of Acid-Base Chemistry* (6th ed.). Chicago, IL: Univ. of Chicago Press, 1974, p. 57.

9. Garella, S., C. L. Dana, and J. A. Chazan. Severity of metabolic acidosis as a determinent of bicarbonate requirements. *N. Engl. J. Med.* 289: 121–126, 1973.

10. Goldberg, M., S. B. Green, M. L. Moss, M. S. Marbach, and D. Garfinkel. Computer-based instruction and diagnosis of acid-base disorders. *J. Am. Med. Assoc.* 223: 269–275, 1973.

11. Hinke, J. A. M., and M. R. Menard. Evaluation of the DMO method for measuring intracellular pH. *Respir. Physiol.* 33: 31–40, 1978.

12. Makoff, D. L. Acid-base metabolism. In: *Clinical Disorders of Fluid and Electrolyte Metabolism* (2nd ed.), edited by M. H. Maxwell and C. R. Kleeman. New York: McGraw-Hill, 1972, p. 297–346.

13. Rasch, R. W. The regulation of acid-base balance—a microprocessor simulation. *Physiologist* 26: 24–28, 1983.

14. Schwartz, W. B., K. J. Orning, and R. Porter. The internal distribution of hydrogen ions with varying degrees of metabolic acidosis. *J. Clin. Invest.* 36: 373–382, 1957.

15. Singer, R. B., J. K. Clark, E. S. Barker, A. P. Crosley, Jr., and J. R. Elkinton. The acute effects in man of rapid intravenous infusion of hypertonic sodium bicarbonate solution. *Medicine* 34: 51–95, 1955.

16. Swan, R. C., and R. F. Pitts. Neutralization of infused acid by nephrectomized dogs. *J. Clin. Invest.* 34: 205–212, 1955.

17. Van Ypersele de Strihou, C., and A. Frans. The respiratory response to chronic metabolic alkalosis and acidosis in disease. *Clin. Sci. Mol. Med.* 45: 439–448, 1973.

18. Waddel, W. J., and T. C. Butler. Calculation of intracellular pH from the distributions of 5,5-dimethyl-2,4-oxazolidine dione (DMO). Application to skeletal muscle. *J. Clin. Invest.* 38: 720–729, 1959.

19. Wiener, F., M. Fayman, U. Teitelman, and S. Bursztein. Computerized medical reasoning in diagnosis and treatment of acid-base disorders. *Crit. Care Med.* 11: 470–475, 1983.

Current Concepts in Photoreceptor Physiology

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Over the past decade and a half research into the workings of the visual system has undergone an enormous increase. In part this increase in vision research is merely a reflection of the great proliferation of biological research in general. But it is also due, I think, to the somewhat unique ability of the visual system to attract scientists with truly diverse interests and motivations from a broad variety of fields. There are, of course, those of us who are actually interested specifically in vision, that is, in how and what an animal sees. However, most vision researchers probably fall into other categories. There are, for example, psychophysicists and sensory physiologists who have interests much broader than the visual sense but who are attracted to vision because of the relatively easy access to the system with a noninvasive, gentle, and extremely well-controlled and quantifiable stimulus. There are the cellular neurophysiologists whose real interests lie in how the brain is organized and how it processes information but who are attracted to the retina as a relatively simple, but not too simple, representative of the brain that is easily isolated and maintained, is exceptionally well-ordered, and is very well-documented histologically. There are also the biochemists who are attracted by the fact that the outer segments of the photoreceptors provide, on the one hand, a membrane preparation that is nearly homogeneous, consisting for the most part, of the visual pigment rhodopsin and, on the other hand, a system that is, once again, easily perturbed by a stimulus in a gentle and controllable manner. Since the photoreceptor is obviously the first cell involved in the visual sense and is therefore the cell whose activity shapes the character of all other neuronal activity throughout the visual system, it is not surprising that much of the attention of all these different types of investigators has turned toward the rods and cones. The result, either from the studies of those directly involved in photoreceptor research or from the provocative questions posed by others who work in different areas of vision, has been an appreciable increase in our understanding of photoreceptor function. This paper will concern itself with three of the more striking advances.[1]

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Phototransduction

Perhaps the most active area of retinal research in recent years has been that concerned with phototransduction—the mechanism by which a photon absorbed by a visual pigment molecule in the outer segment of the photoreceptor is converted to an electrical signal that has meaning to the nervous system. The absorption of the photon isomerizes the chromophore of the visual pigment and thereby initiates a very complex sequence of conformational changes in the visual pigment molecule that manifest themselves in the form of spectral intermediates. It is not known with any degree of certainty which one of the intermediates sets into motion the events that will change the conductance of the plasma membrane of the photoreceptor. What is much more certain is that the primary electrical change due to a light stimulus is the result of a decrease in cationic flux across a light-sensitive channel (81, 84, 90). This flux, which is comprised of inward-moving sodium ions and outward-moving potassium and calcium ions (90), is such that in the dark there is a net inward movement of positive charge, and therefore the unstimulated photoreceptor is relatively depolarized with a membrane potential of only about -30 or -40 mV. Upon absorption of a photon, this light-sensitive conductance decreases, causing the membrane to hyperpolarize. This hyperpolarization is the photoreceptor potential from which all other neural events in the retina ensue (80). A major problem in the process stems from the fact that most of the rhodopsin is located in the disc membranes of the rod outer segment and, without doubt, almost all light absorption occurs within one or another of these discs which constitute an extremely effective light trap. These discs are for the most part, however, separated from the plasma membrane of the rod where the dark conductance decreases, and it therefore seems necessary to invoke the presence of a substance that can diffuse from the disc to the plasma membrane—an internal transmitter. Yoshikami and Hagins (92) first made the suggestion that the internal transmitter is calcium, a suggestion that has strong appeal to those physiologists who are generalists, since calcium plays an indispensable role as messenger in neurotransmission, excitation coupling, and the like. An enormous amount of time and effort has subsequently been devoted to trying to implicate calcium in or eliminate it from a role in the phototransduction process. Over the years the results have been less than consistent, sometimes quite contradictory, and often confusing. However, several things can now be said with a fair degree of certainty. It has been known for some time, for example, that the amplitude of the receptor response to light in both rods and cones is inversely related to external calcium concentration (5, 7,

[1] A discussion of the advances made in invertebrate photoreception is beyond the scope of this paper. For readers interested in invertebrates I recommend the review by Hillman et al. (43) and the symposium volume edited by Ali (1). For readers who wish to place this review in a somewhat broader perspective, I recommend the monograph by Fein and Szuts (29).

10, 69, 70, 87). There is reason to believe that this is due to a suppression of dark current which reflects a decrease in the cationic conductance across the light-sensitive channel (40). Thus the action of calcium would appear to mimic the effect of light on the photoreceptor, at least insofar as a qualitative decrease in dark conductance is concerned, and this is certainly consistent with the concept of calcium serving as the internal transmitter. Also consistent is the recent evidence that exposure of intact photoreceptors to light results in a significant increase in extracellular calcium (35, 36, 91). The rate of this increase is directly proportional to the intensity of the light stimulus. Moreover, the increase in external calcium can be induced by light even under conditions where the receptor potential has been eliminated by the removal of external sodium, indicating that the light-dependent release of calcium precedes the receptor response and is not simply due to that electrical change (36). All of this has meaning, insofar as acceptance of calcium as the internal transmitter is concerned, only if one accepts the proposition that the increase in external calcium is a reflection of a like increase in cytoplasmic calcium which, in turn, has resulted from a release of calcium from the internal discs in response to light. This certainly is not unreasonable; however, as yet there is still no convincing direct biochemical evidence that a light stimulus causes an increase in intracellular calcium that is both large enough and fast enough to explain the photoreceptor response to light. Moreover, the effects of alterations in calcium concentration do not correlate well with respect to light's influence on receptor sensitivity and response kinetics (3). Thus the idea that calcium by itself serves as the internal transmitter responsible for generating the photoreceptor potential remains intriguing and quite possible but is far from a proven fact.

The inadequacies of the calcium hypothesis have, in recent years, caused many to gravitate toward an alternative idea, that transduction in the photoreceptor is dependent on a cyclic nucleotide system. The basic idea here is essentially that guanosine 3',5'-cyclic monophosphate (cGMP) maintains conductance in the dark, presumably by maintaining a set degree of phosphorylation of small membrane proteins located in the light-sensitive channels. Light might act by decreasing cGMP concentration, thereby decreasing conductance and hyperpolarizing the photoreceptor (8, 26). Certainly there is little doubt now that cyclic nucleotides are somehow very important to the generation of the receptor potential. There is a large amount of cGMP in the retina, and most of it is in the outer segments of the rods (21, 27, 30, 38, 66, 85). Moreover, exposure to bright light definitely results in a large decrease in cGMP concentration (14, 21, 28, 30, 37, 51, 85) and, most importantly, this decrease appears to precede the light-induced conductance change that occurs at the plasma membrane (19). Indeed, there is a light-activated phosphodiesterase in rod photoreceptors that is closely associated with rhodopsin and in fact requires rhodopsin for binding to the disc membrane (6, 50, 60, 90). Bright light causes this phosphodiesterase to be activated to many times its dark level, and this could very well explain the action of bright light in reducing cGMP concentration (54, 55). Provided the phosphodiesterase in the dark is more sensitive to the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX) than is the light-activated phosphodiesterase, this is all consistent with the observations that IBMX causes depolarization of the rods in the dark, an increase in receptor potential amplitude in response to light, and an increase in photoreceptor sensitivity (11, 12, 42, 56, 84). It is as if IBMX, by increasing the concentration of cGMP, has made the rod more dark adapted. In fact, increasing the intracellular concentration of cGMP by microinjection does cause depolarization of the rod photoreceptor (61, 63, 65). Moreover, both the effects of IBMX and the effects of cGMP injection are reversed by light. This is all well and good, but unfortunately there are some problems that remain and that cast doubt on cGMP as the sole mediator of phototransduction.

One problem is that, in contrast to the experiments with bright light, experiments with dim light (which can be viewed as the more physiological condition) have not produced major sustained changes in cGMP concentration either in the intact retina or in isolated outer segments (38, 51). This is not consistent with the rod photoreceptor's exquisite light sensitivity and relatively short latency in response to a dim light stimulus. However, although a problem, this may simply reflect a lack of sensitivity in the analytical methods employed (38, 51). Much more serious is the fact that changes in the intracellular concentration of cGMP do not appear to be very well correlated with light-induced changes in conductance or with responsivity of rod photoreceptors (59, 67, 86). Moreover, in a recent study on voltage-clamped rods, it was shown that the reversal voltage for the conductance induced by intracellular injection of cGMP is very different from the reversal voltage for the conductance induced by light (71).

It becomes clear from all this that neither calcium alone nor cGMP alone can explain phototransduction. It is also clear, however, that both are very important to the photoreceptor response. Since calcium and cGMP do appear to interact, it is not unreasonable to suppose that both are involved in and vital to the mechanism of transduction. A typical scheme relating cGMP and calcium activity is illustrated in Figure 1. In this scheme, a photon of light is absorbed by a molecule of rhodopsin, which is then converted to an active form. This activated rhodopsin in turn activates a guanosine 5'-triphosphate (GTP) binding protein, called (I think somewhat hopefully) transducin by some, which then binds GTP (31). The transducin-GTP complex then activates the membrane-bound phosphodiesterase which hydrolyzes cGMP and, in so doing, somehow causes the release of calcium from a site within or on the disc. The calcium diffuses to the plasma membrane where it somehow blocks the dark conductance, causing the membrane to hyperpolarize. A model such as this is attractive for several reasons. First, it is consistent with the nature of enzymatic cascades in other systems. Second, it easily accounts for the amplification necessary to explain how a single photon can cause a large change in the dark conductance. Third, it reconciles two extreme points of view by designating important and interrelated roles for both calcium and cyclic nucleotides, a situation which even intuitively makes a good deal of sense. This is not to say that the scheme as it stands can explain all that is known about the response characteristics of the photoreceptors. The question of how calcium would actually close the light-sensitive channels is still left to the imagination. In fact, we still do not really know if cytoplasmic calcium increases in response to light. Calcium may prove to

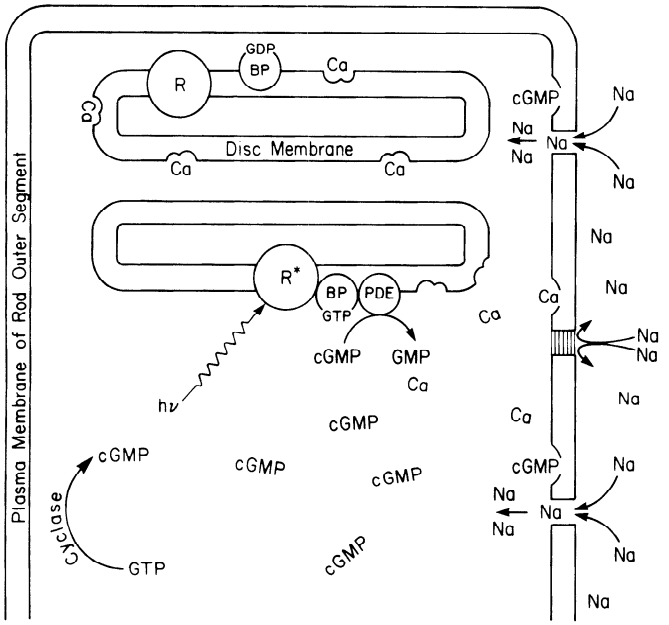

Figure 1

Phototransduction in the rod photoreceptor—a hypothetical scheme. Light is absorbed by a rhodopsin molecule (R*), which then activates GTP binding protein or transducin (BP). GTP binding protein then activates phosphodiesterase (PDE), resulting in the hydrolysis of cGMP with the consequent release of calcium ions (Ca) from their sites within or on the outer segment disc. Calcium ions move down their diffusion gradient to the plasma membrane where they displace cGMP from binding sites associated with light-sensitive channels. Displacement of cGMP closes the channel and decreases cationic conductance, leading to hyperpolarization of the cell. Na is used to designate net influx of positive charges across the light-sensitive channel in the dark, since this influx is due to sodium ions. It is not meant to imply that only sodium ions traverse the light-sensitive channel (see text and Ref. 88). Redrawn and revised from Ref. 62.

be important only in its role in the sodium-calcium exchanger mechanism that recently has been demonstrated in rods (89). And the model only applies directly to rod photoreceptors; the cones are a mystery that investigators for the most part have not even attempted to solve. It will therefore come as no great surprise if the model is substantially modified, or even replaced, as a result of new research in the next year or two. Nevertheless, the model is based on hard data and is workable. It reflects a degree of understanding of phototransduction that was beyond the imagination just a few years ago. [For a comprehensive analysis of phototransduction the reader should consult the superb review by Korenbrot (52).]

A Photoreceptor Syncitium

Much of what is known about the electrical response to light, with which biochemical experiments on phototransduction are compared, comes from studies where single rods have been impaled with superfine microelectrodes. The interpretation of data from such studies has generally assumed that the impaled photoreceptor behaves as an entirely independent entity. Of course, interaction of photoreceptors via horizontal cells was recognized as a potential problem, but this was dealt with easily through the use of chemical agents, such as cobalt or aspartate, which interfere with chemical neurotransmission. Now, however, it has become clear that rods do not function independently but, rather, are coupled and function as part of a network or syncitium (16, 17, 24, 32, 33, 39, 68, 76–78). Obviously, this has serious repercussions both for the meaning of previous data and for our understanding of how the photoreceptor is processing visual information. Recognition of the existence of a syncitium has therefore led to increasingly more widespread use of the suction electrode technique, a powerful method that allows examination of the electrical characteristics of single isolated photoreceptors (e.g., Refs. 4, 15, 18, 19, 47, 57, 58, 75, 87–89).

That the rods are indeed coupled can be seen from the experiment illustrated in Figure 2. In this experiment Owen and Copenhagen (68) impaled two turtle rods simultaneously. Injection of current into one rod caused a voltage change in the other rod. Likewise, injection of current into the second rod resulted in a voltage change in the first rod. Current injected into the extracellular space had no effect, showing that the two rods were indeed coupled. The coupling conductance is rectified in that hyperpolarizing currents are much more effective than depolarizing currents. This makes good sense if coupling is to have physiological meaning, since the normal response of the photoreceptors is one of hyperpolarization. The coupling between rods is not affected by treatment with cobalt, leading to the conclusion that the coupling conductance is not mediated through a chemical synapse but, rather, is electrical in nature (68). In fact, studies with the electron microscope reveal the presence of classical gap junctions between adjacent rods (33, 34). This is not to say that rod-rod coupling is dependent on the rods being in very close proximity to one another. For example, in the turtle retina there are many cones and the density of rods is rather low (68). In fact, Owen and Copenhagen (68) reported that almost all of the coupled rods from which they recorded were separated by at least 120 μm, the equivalent of several intervening photoreceptors. It was suggested, and it does seem likely, that the relatively long and extensive teleodendritic processes of the turtle rods are responsible for the rod-rod coupling in the turtle retina (68).

In any case, it becomes obvious that the rod photoreceptor cannot any longer be treated as an individual

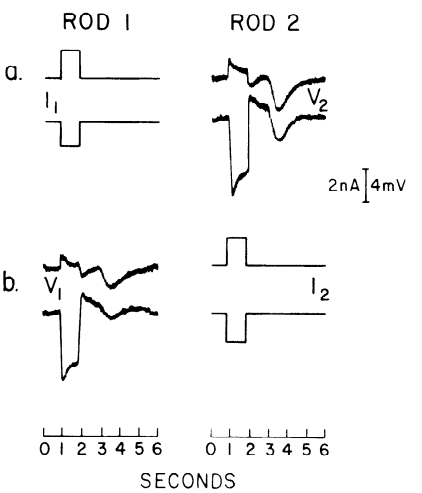

Figure 2

Electrical coupling of rod photoreceptors. *Rods 1* and *2* were impaled simultaneously with microelectrodes. Passage of current through *rod 1* (I_1) led to a voltage change in *rod 2* (V_2). Passage of current through *rod 2* (I_2) led to a voltage change in *rod 1* (V_1). Flow of current is rectified in that hyperpolarizing current (downward square pulse) was much more effective than depolarizing current (upward square pulse). Slow hyperpolarizations following the potential changes induced by current injection in the neighboring rod are responses to a light stimulus. Redrawn from Ref. 68.

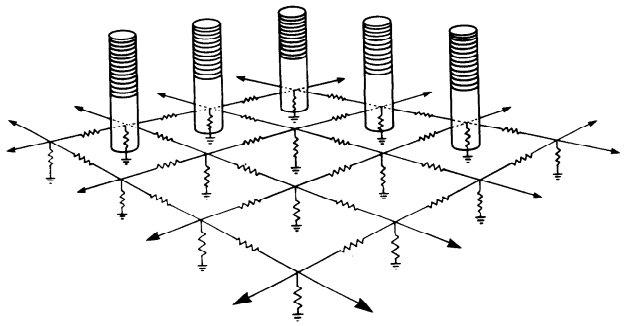

Figure 3

Photoreceptor syncitium. Rods do not behave as independent entities but, rather, are electrically coupled to one another in a network which may involve thousands of cells. Redrawn from Ref. 33.

but must now be considered as part of a rather extensive photoreceptor network, perhaps similar to that illustrated in Figure 3, and this is going to seriously complicate the interpretation of the physiological meaning of the absorption of a photon. For example, a glance at Figure 3 should make it clear that the voltage change due to the absorption of a photon by one of the rods in the network will generate a current which is not restricted to the absorbing rod (as previously believed) but, rather, is shunted across the coupling resistance of the other rods in the syncitium.

It is not yet clear exactly what consequences such shunting will have with respect to signal transmission. One could argue that any shunting of current away from the photostimulated rod will of necessity reduce the current available for signaling at the synapse of the rod with the more proximal retinal neurons. One could also argue that in such a highly convergent system, where many rods synapse onto the same bipolar cell, current loss in one rod is simply compensated for by current gain in a neighboring rod and that, therefore, the signal at the synapse is not seriously affected by the syncitium. It might even be possible that the shunted current somehow initiates an active electrical event in the rods coupled to the photostimulated cell and, as a result, there is a net increase in the magnitude of the signal to a common bipolar cell. The possibility of an enhancement effect was raised by Falk and Fatt (25), who concluded that the synaptic signal which results from absorption of a single photon by a single rod could not be sorted out from the noise intrinsic to the system. This is especially important, since it is rather generally accepted that the human can perceive on the order of a single photon. Actually, it can be reasoned that, under the right conditions, the rod syncitium can reduce the effect of intrinsic noise which is due to random current generation in the photoreceptor, probably as a result of spontaneous thermal denaturation of rhodopsin. If, for example, a random event occurs in one rod within the network, the current generated will be shunted and therefore the effect within that rod will be reduced and perhaps diminished even at the rod-bipolar synapse. On the other hand, a diffuse stimulus of moderate intensity might stimulate each rod in the syncitium. Under these conditions, the rods would remain isopotential to one another and no shunting would occur. The net effect of the syncitium, then, would be to reduce noise while not affecting the response to light and therefore the signal-to-noise ratio in the rod system would be increased—certainly a desirable effect. However, near the visual threshold, where only a few isolated rods would absorb a photon, the rod network would not remain isopotential and the current generated by the light would be shunted in the same manner as the current associated with random noise. Near the visual threshold, it is therefore hard to see how the rod syncitium would improve the signal-to-noise ratio. And, after all, it is at the visual threshold where increasing the signal-to-noise ratio would seem to be most valuable.

Another problem with a photoreceptor syncitium is that it must undoubtedly reduce spatial resolution, since an otherwise discrete well-localized event in the retina is now spread out over a relatively large field. Perhaps in the rod system this is not really important, because the system is highly convergent anyway, and so is not noted for its ability to provide the animal with high resolving power. However, cone photoreceptors are important to acute vision, and they are also now known to be electrically coupled in a manner analogous to rods (22). It is difficult to reconcile the function of the cones with the existence of a cone syncitium. It is therefore of great interest that both rod-cone coupling and cone-cone coupling have recently been reported in the retina of a species of squirrel (41) believed to depend on acute vision for its survival. Examination of photoreceptor coupling in other cone-dominant retinas, such as those of birds, would be important, and a comparison of the foveal and nonfoveal cones of the primate retina would be especially welcome. [For detailed analysis of photoreceptor coupling the reader should consult the excellent reviews by Owen and Copenhagen (68) and by Gold (33).]

The Signal at the Synapse

Transmission of information from the photoreceptors to the second-order neurons of the retina is believed to be mediated by a classical chemical synapse. As yet, no single substance has been unequivocally identified as a neurotransmitter at this synapse. However, there is now a goodly amount of evidence to indicate that excitatory amino acids, in particular L-glutamate, are involved (2, 9, 44–46, 53). Certainly, as shown in Figure 4, low concentrations of L-glutamate are capable of depolarizing horizontal cells (44–46, 53, 64). And histochemical studies show that glutamate is concentrated in the synaptic terminals of at least some photoreceptors (9). If, in fact, the chemical synapse between the photoreceptors and the second-order retinal neurons functions in the manner typical of all other chemical synapses, then it is

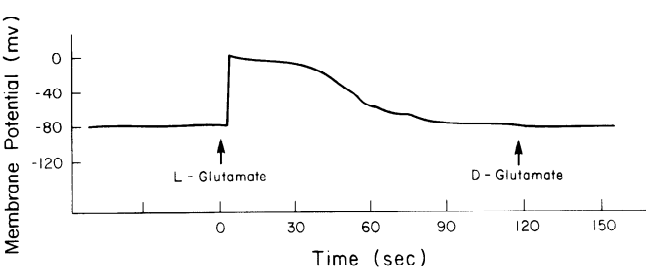

Figure 4

Depolarization of a horizontal cell. L-Glutamate causes an isolated cultured horizontal cell to depolarize. Effect is very specific and even D-glutamate has no influence. Experiments such as this support L-glutamate as a leading candidate for the neurotransmitter released by the photoreceptor. Redrawn from Ref. 53.

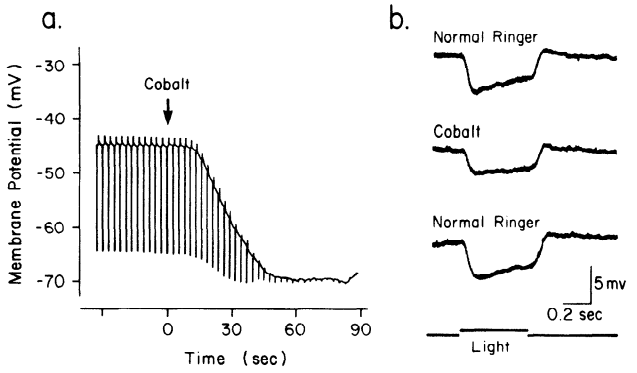

Figure 5
Effect of cobalt on photoreceptors and horizontal cells. Cobalt, a substance that inhibits neurotransmitter release, causes the horizontal cell to hyperpolarize (*a*), thus mimicking the effect of light. However, cobalt has little influence on the electrical response of the photoreceptor (*b*). This experiment supports the idea that the photoreceptor continuously releases transmitter in the dark and that the action of light is to inhibit transmitter release. Redrawn from Ref. 49.

not unreasonable to assume that depolarization of the photoreceptor leads to release of L-glutamate, which then depolarizes the horizontal cells. However, the photoreceptor is depolarized in the dark and the effect of a light stimulus is to hyperpolarize the cell. This means that the neurotransmitter would be released continuously in the dark and the effect of light would be to decrease neurotransmitter release.

The suggestion that the signal at the photoreceptor synapse is a reduction in transmitter release was first made by Trifonov (83), who showed that depolarization of the photoreceptor with transretinal current causes depolarization of the horizontal cells. There is now a substantial body of additional information to support this hypothesis. For example, cobalt (Figure 5) and magnesium, substances known to inhibit transmitter release at chemical synapses, mimic the effects of light on the electrical activity of both bipolar and horizontal cells (13, 20, 23, 48, 49). Conversely, lanthanum, which accelerates neurotransmitter release, causes depolarization of horizontal cells and therefore mimics the effect of darkness (48, 49). Moreover, these pharmacologically induced changes in electrical activity are consistent with effects of light on the resistance and conductance of the postsynaptic membranes, providing transmitter is released in the dark and the release is impeded by light (20, 49, 81, 82). Finally, studies with horseradish peroxidase (HRP) indicate that the synaptic activity of photoreceptors is greatest in the dark. Light blocks the uptake of HRP by the synaptic vesicles in the photoreceptor terminals (72–74). The fact that HRP uptake by the photoreceptors is blocked by magnesium also lends further support to the conclusions drawn from the electrophysiological experiments with both magnesium and cobalt (72). There is now general acceptance, therefore, that the photoreceptor's response to light is signaled to the secondary retinal neurons by a decrease in neurotransmitter release.

Summary

Great strides have been made in recent years regarding our understanding of photoreceptor physiology. We know that the photoreceptor responds to light with a hyperpolarization that is due to a decrease in cationic flux across a light-sensitive channel. This conductance decrease is brought about via a transduction mechanism that involves cyclic nucleotides and calcium. The photoreceptors can no longer be viewed as behaving independently but, rather, function in the manner of a syncitium, perhaps as a means of improving the signal-to-noise ratio. In response to light, photoreceptors signal the secondary neurons to which they are connected by decreasing the neurotransmitter that they continuously release in the dark. A likely candidate for the transmitter released by the photoreceptors, at least in some retinas, is L-glutamate.

References

1. Ali, M. A. *Photoreception and Vision in Invertebrates.* New York: Plenum, 1984.

2. Altschuler, R. A., J. L. Mosinger, G. G. Harmison, M. H. Parakkal, and R. J. Wenthold. Aspartate aminotransferase-like immunoreactivity as a marker for aspartate/glutamate in guinea pig photoreceptors. *Nature London* 298: 657–659, 1982.

3. Bastian, B. L., and G. L. Fain. Light adaptation in toad rods: requirement for an internal messenger which is not calcium. *J. Physiol. London* 297: 493–520, 1979.

4. Baylor, D. A., T. D. Lamb, and K.-W. Yau. The membrane current of single rod outer segments. *J. Physiol. London* 288: 589–611, 1979.

5. Bertrand, D., M. G. F. Fuortes, and J. Pochobradsky. Actions of EGTA and high calcium on the cones in the turtle retina. J. Physiol. London 275: 419–437, 1978.

6. Bitensky, M. W., G. L. Wheeler, B. Aloni, S. Vetury, and Y. Matuo. Light- and GTP-activated photoreceptor phosphodiesterase: regulation by a light-activated GTPase and identification of rhodopsin as the phosphodiesterase binding site. *Adv. Cyclic Nucleotide Res.* 9: 553–572, 1978.

7. Bolnick, D. A., E. W. Clinite, A. E. Walter, and A. J. Sillman. The influence of calcium on the aspartate-isolated mass receptor potential of bullfrog cones. *Curr. Eye Res.* 1: 57–64, 1981.

8. Bownds, M. D. Biochemical steps in visual transduction: roles for nucleotides and calcium ions. *Photochem. Photobiol.* 32: 487–490, 1980.

9. Brandon, C., and D. M.-K. Lam. L-Glutamic acid: a neurotransmitter candidate for cone photoreceptors in human and rat retinas. *Proc. Natl. Acad. Sci. USA.* 80: 5117–5121, 1983.

10. Brown, J. E., and L. H. Pinto. Ionic mechanism for the photoreceptor potential of the retina of *Bufo marinus. J. Physiol. London* 236: 575–591, 1974.

11. Brown, J. E., and G. Waloga. Effects of cyclic nucleotides and calcium ions on *Bufo* rods. *Curr. Topics Membr. Transp.* 15: 369–380, 1981.

12. Capovilla, M., L. Cervetto, and V. Torre. The effect of phosphodiesterase inhibitors on the electrical activity of toad rods. *J. Physiol. London* 343: 277–294, 1983.

13. Cervetto, L., and M. Piccolino. Synaptic transmission between photoreceptors and horizontal cells in the turtle retina. *Science* 183: 417–419, 1974.

14. Cohen, A. I., I. A. Hall, and J. A. Ferrendelli. Calcium and cyclic nucleotide regulation in incubated mouse retinas. *J. Gen. Physiol.* 71: 595–612, 1978.

15. Conner, J. D. The relation between excitation and adaptation within the rod's outer segment. *Neurosci. Lett.* 30: 245–250, 1982.

16. Copenhagen, D. R., and W. G. Owen. Coupling between rod photoreceptors in a vertebrate retina. *Nature London* 260: 57–59, 1976.

17. Copenhagen, D. R., and W. G. Owen. Functional characteristics of lateral interactions between rods in the retina of the snapping turtle. *J. Physiol. London* 259: 251–282, 1976.

18. Cornwall, M. C., A. Fein, and E. F. MacNichol. Spatial localization of bleaching adaptation in isolated vertebrate rod photoreceptors. *Proc. Natl. Acad. Sci. USA* 80: 2785–2788, 1983.

19. Cote, R. H., M. S. Biernbaum, G. D. Nicol, and M. D. Bownds. Light-induced decreases in cGMP concentration precede changes in membrane permeability in frog rod photoreceptors. *J. Biol. Chem.* 259: 9635–9641, 1984.

20. Dacheux, R. F., and R. F. Miller. Photoreceptor-bipolar cell transmission in the perfused retina eyecup of the mudpuppy. *Science* 191: 963–964, 1976.

21. DeAzerado, F. A. M., W. D. Lust, and J. V. Passonneau. Light-induced changes in energy metabolites, guanine nucleotides and guanylate cyclase within frog retinal layers. *J. Biol. Chem.* 256: 2731–2735, 1981.

22. Detwiler, P. B., and A. L. Hodgkin. Electrical coupling between cones in turtle retina. *J. Physiol. London* 291: 75–100, 1979.

23. Dowling, J. E., and H. Ripps. Effect of magnesium on horizontal cell activity in the skate retina. *Nature London* 242: 101–103, 1973.

24. Fain, G. L. Quantum sensitivity of rods in the toad retina. *Science* 187: 838–841, 1975.

25. Falk, G., and P. Fatt. Physical changes induced by light in the rod outer segment of vertebrates. In: *Handbook of Sensory Physiology*, edited by H. J. A. Dartnall. New York: Springer-Verlag, 1972, vol. 7, pt. 1, pp. 200–244.

26. Farber, D. B., B. M. Brown, and R. N. Lolley. Cyclic GMP: proposed role in visual cell function. *Vision Res.* 18: 497–499, 1978.

27. Farber, D. B., and R. N. Lolley. Cyclic guanosine monophosphate: elevation in degenerating photoreceptor cells of the C3H mouse retina. *Science* 186: 449–451, 1974.

28. Farber, D. B., and R. N. Lolley. Light-induced reduction in cyclic GMP of retinal photoreceptor cells *in vivo*: abnormalities in the degenerative diseases of RCS rats and *rd* mice. *J. Neurochem.* 28: 1089–1095, 1977.

29. Fein, A., and E. Z. Szuts. *Photoreceptors, Their Role in Vision.* New York: Cambridge Univ. Press, 1982.

30. Ferrendelli, J. A., and A. I. Cohen. The effects of light and dark adaptation on the levels of cyclic nucleotides in retinas of mice heterozygous for a gene for photoreceptor dystrophy. *Biochem. Biophys. Res. Commun.* 73: 421–427, 1976.

31. Fung, B. K.-K., J. B. Hurley, and L. Stryer. Flow of information in the light-triggered cyclic nucleotide cascade of vision. *Proc. Natl. Acad. Sci. USA* 78: 152–156, 1981.

32. Gold, G. H. Photoreceptor coupling in retina of the toad, *Bufo marinus*. II. Physiology. *J. Neurophysiol.* 42: 311–328, 1979.

33. Gold, G. H. Photoreceptor coupling: its mechanism and consequences. *Curr. Topics Membr. Transp.* 15: 59–89, 1981.

34. Gold, G. H., and J. E. Dowling. Photoreceptor coupling in retina of the toad, *Bufo marinus*. I. Anatomy. *J. Neurophysiol.* 42: 292–310, 1979.

35. Gold, G. H., and J. I. Korenbrot. Light-induced calcium release by intact retinal rods. *Proc. Natl. Acad. Sci. USA* 77: 5557–5561, 1980.

36. Gold, G. H., and J. I. Korenbrot. The regulation of calcium in the intact retinal rod: a study of light-induced calcium release by the outer segment. *Curr. Topics Membr. Transp.* 15: 307–330, 1981.

37. Goridis, C., P. F. Urban, and P. Mandel. The effect of flash illumination on the endogenous cyclic GMP content of isolated frog retinae. *Exp. Eye Res.* 24: 171–177, 1977.

38. Govardovskii, V. I., and A. L. Berman. Light-induced changes of cyclic GMP content in frog retinal rod outer segments measured with rapid freezing and microdissection. *Biophys. Struct. Mech.* 7: 125–130, 1981.

39. Griff, E. R., and L. H. Pinto. Interactions among rods in the isolated retina of *Bufo marinus*. *J. Physiol. London* 314: 237–254, 1981.

40. Hagins, W. A. The visual process: excitatory mechanisms in the primary receptor cells. *Annu. Rev. Biophys. Bioeng.* 1: 131–158, 1972.

41. Hara, S., and M. Miyoshi. Gap junctions between visual cells in the squirrel retina. *Biomed. Res.* 5: 101–110, 1984.

42. Haynes, L. W., and A. J. Sillman. Concentration dependent effects of 3-isobutylmethylxanthine on the responses of bullfrog rods and cones. Unpublished observations.

43. Hillman, P., S. Hochstein, and B. Minke. Transduction in invertebrate photoreceptors: role of pigment bistability. *Physiol. Rev.* 63: 668–772, 1983.

44. Ishida, A. T. Responses of solitary retinal horizontal cells to L-glutamate and kainic acid are antagonized by D-aspartate. *Brain Res.* 298: 25–32, 1984.

45. Ishida, A. T., and G. L. Fain. D-Aspartate potentiates the effects of L-glutamate on horizontal cells in goldfish retina. *Proc. Natl. Acad. Sci. USA* 78: 5890–5894, 1981.

46. Ishida, A. T., A. Kaneko, and M. Tachibana. Solitary horizontal cells in culture. II. A new tool for examining effects of photoreceptor neurotransmitter candidates. *Vision Res.* 23: 1217–1220, 1983.

47. Jagger, W. S. Photoresponses of isolated frog rod outer segments. *Vision Res.* 19: 159–167, 1979.

48. Kaneko, A., and H. Shimazaki. Effects of external ions on the synaptic transmission from photoreceptors to horizontal cells in the carp retina. *J. Physiol. London* 252: 509–522, 1975.

49. Kaneko, A., and H. Shimazaki. Synaptic transmission from photoreceptors to bipolar and horizontal cells in the carp retina. *Cold Spring Harbor Symp. Quant. Biol.* 40: 537–546, 1976.

50. Kawamura, S., and M. D. Bownds. Light adaptation of the cyclic GMP phosphodiesterase of frog photoreceptor membranes mediated by ATP and calcium ions. *J. Gen. Physiol.* 77: 571–591, 1981.

51. Kilbride, P., and T. G. Ebrey. Light-initiated changes of cyclic guanosine monophosphate levels in the frog retina measured with quick-freezing techniques. *J. Gen. Physiol.* 74: 415–426, 1979.

52. Korenbrot, J. I. Signal mechanisms of phototransduction in retinal rods. *CRC Crit. Rev. Biochem.* In press.

53. Lasater, E. M., and J. E. Dowling. Carp horizontal cells in culture respond selectively to L-glutamate and its agonists. *Proc. Natl. Acad. Sci. USA* 79: 936–940, 1982.

54. Liebman, P. A., and E. N. Pugh, Jr. ATP mediates rapid reversal of cyclic GMP phosphodiesterase activation in visual receptor membranes. *Nature London* 287: 734–736, 1980.

55. Liebman, P. A., and E. N. Pugh, Jr. Control of rod disk membrane phosphodiesterase and a model for visual transduction. *Curr. Topics Membr. Transp.* 15: 157–170, 1981.

56. Lipton, S. A., H. Rasmussen, and J. E. Dowling. Electrical and adaptive properties of rod photoreceptors in *Bufo marinus*. II. Effects of cyclic nucleotides and prostaglandins. *J. Gen. Physiol.* 70: 771–791, 1977.

57. Matthews, G. Physiological characteristics of single green rod photoreceptors from toad retina. *J. Physiol. London* 342: 347–359, 1983.

58. Matthews, G., Photocurrents of single retinal rods from *Rana pipiens* tadpoles. *Vision Res.* 24: 821–825, 1984.

59. Meyertholen, E. P., M. J. Wilson, and S. E. Ostroy. Removing bicarbonate/CO_2 reduces the cGMP concentration of the vertebrate photoreceptor to the levels normally observed on illumination. *Biochem. Biophys. Res. Commun.* 96: 785–792, 1980.

60. Miki, N., J. M. Baraban, J. J. Keirns, J. J. Boyce, and M. W. Bitensky. Purification and properties of the light-activated cyclic nucleotide phosphodiesterase of rod outer segments. *J. Biol. Chem.* 250: 6320–6327, 1975.

61. Miller, W. H. Physiological evidence that light-mediated decrease in cyclic GMP is an intermediary process in retinal rod transduction. *J. Gen. Physiol.* 80: 103–123, 1982.

62. Miller, W. H. Does cyclic GMP hydrolysis control visual transduction in rods? *Trends Pharmacol. Sci.* 4: 509–511, 1983.

63. Miller, W. H., and G. D. Nicol. Evidence that cyclic GMP regulates membrane potential in rod photoreceptors. *Nature London* 280: 64–66, 1979.

64. Murakami, M., K. Ohtsu, and T. Ohtsuka. Effects of chemicals on receptors and horizontal cells in the retina. *J. Physiol. London* 227: 899–913, 1972.

65. Nicol, G. D., and W. H. Miller. Cyclic GMP injected into retinal rod outer segments increases latency and amplitude of response to illumination. *Proc. Natl. Acad. Sci. USA* 75: 5217–5220, 1978.

66. Orr, H. T., O. H. Lowry, A. I. Cohen, and J. A. Ferrendelli. Distribution of 3':5'-cyclic AMP and 3':5'-cyclic GMP in rabbit retina *in vivo*: selective effects of dark and light adaptation and ischemia. *Proc. Natl. Acad. Sci. USA* 73: 4442–4445, 1976.

67. Ostroy, S. E., E. P. Meyertholen, P. J. Stein, R. A. Svoboda, and M. J. Wilson. Limits on the role of rhodopsin and cGMP in the functioning of the vertebrate photoreceptor. *Curr. Topics Membr. Transp.* 15: 393–404, 1981.

68. Owen, W. G., and D. R. Copenhagen. Characteristics of the electrical coupling between rods in the turtle retina. In: *Vertebrate Photoreception*, edited by H. B. Barlow and P. Fatt. San Francisco, CA: Academic, 1977, p. 169–192.

69. Pautler, E. L., and D. V. Sturges. The effect of calcium on the cone late receptor potential. *Exp. Eye Res.* 13: 178–180, 1972.

70. Pautler, E. L., and H. Su. The effect of calcium on the distal PIII component of the frog ERG. *Exp. Eye Res.* 12: 70–79, 1971.

71. Pinto, L. H., and J. E. Brown. Pressure injection of 3',5'-cyclic GMP into solitary rod photoreceptors of the tiger salamander. *Brain. Res.* 304: 197–200, 1984.

72. Ripps, H., M. Shakib, and E. D. MacDonald. Peroxidase uptake by photoreceptor terminals of the skate retina. *J. Cell Biol.* 70: 86–96, 1976.

73. Schacher, S. M., E. Holtzman, and D. C. Hood. Uptake of horseradish peroxidase by frog photoreceptor synapses in the dark and the light. *Nature London* 249: 261–263, 1974.

74. Schacher, S., E. Holtzman, and D. C. Hood. Synaptic activity of frog retinal photoreceptors. A peroxidase uptake study. *J. Cell Biol.* 70: 178–192, 1976.
75. Schnapf, J. L. Dependence of the single photon response on longitudinal position of absorption in toad rod outer segments. *J. Physiol. London* 343: 147–159, 1983.
76. Schwartz, E. A. Responses of single rods in the retina of the turtle. *J. Physiol. London* 232: 503–514, 1973.
77. Schwartz, E. A. Rod-rod interaction in the retina of the turtle. *J. Physiol. London* 246: 617–638, 1975.
78. Schwartz, E. A. Electrical properties of the rod syncitium in the retina of the turtle. *J. Physiol. London* 257: 379–406, 1976.
79. Sillman, A. J., H. Ito, and T. Tomita. Studies on the mass receptor potential of the isolated frog retina. II. On the basis of the ionic mechanism. *Vision Res.* 9: 1443–1451, 1969.
80. Tomita, T. Electrical activity of vertebrate photoreceptors. *Q. Rev. Biophys.* 3: 179–222, 1970.
81. Toyoda, J.-I. Membrane resistance changes underlying the bipolar cell response in the carp retina. *Vision Res.* 13: 283–294, 1973.
82. Toyoda, J.-I., H. Nosaki, and T. Tomita. Light-induced resistance changes in single photoreceptors of *Necturus* and *Gekko*. *Vision Res.* 9: 453–463, 1969.
83. Trifonov, Y. A. Study of synaptic transmission between the photoreceptor and the horizontal cell using electrical stimulation of the retina. *Biofizika* 13: 809–817, 1968.
84. Waloga, G. Effects of calcium and guanosine-3':5'-cyclic-monophosphoric acid on receptor potentials of toad rods. *J. Physiol. London* 341: 341–357, 1983.
85. Woodruff, M. L., and M. D. Bownds. Amplitude, kinetics, and reversibility of a light-induced decrease in guanosine 3',5'-cyclic monophosphate in frog photoreceptor membranes. *J. Gen. Physiol.* 73: 629–653, 1979.
86. Woodruff, M. L., and G. L. Fain. Ca^{2+}-dependent changes in cyclic GMP levels are not correlated with opening and closing of the light-dependent permeability of toad photoreceptors. *J. Gen. Physiol.* 80: 537–555, 1982.
87. Yau, K.-W., P. A. McNaughton, and A. L. Hodgkin. Effect of ions on the light-sensitive current in retinal rods. *Nature London* 292: 502–505, 1981.
88. Yau, K.-W., and K. Nakatani. Cation selectivity of light-sensitive conductance in retinal rods. *Nature London* 309: 352–354, 1984.
89. Yau, K.-W., and K. Nakatani. Electrogenic Na-Ca exchange in retinal rod outer segment. *Nature London* 311: 661–663, 1984.
90. Yee, R., and P. A. Liebman. Light-activated phosphodiesterase of the rod outer segment. Kinetics and parameters of activation and deactivation. *J. Biol. Chem.* 253: 8902–8909, 1978.
91. Yoshikami, S., J. S. George, and W. A. Hagins. Light-induced calcium fluxes from outer segment layer of vertebrate retinas. *Nature London* 286: 395–398, 1980.
92. Yoshikami, S., and W. A. Hagins. Light, calcium and the photocurrent of rods and cones. *Biophys. Soc. Abstr.* 15: 47, 1971.

Book Review

A Guide to Biomedical Research.

T. M. E. Davis

Boston: Blackwell, 1984, 93 pp, index, $9.00

This little book (less than one hundred 4½ × 6¾ inch pages) is a primer for the graduate student. It takes up in a logical order the aspects of involvement in a beginning research career which are important and which most of us have learned through (sometimes distasteful) experience.

The language is direct and simple and presented with a mild degree of humor

The subjects covered range from practical matters such as choice of a research supervisor, laboratory environment, and research topics to conceptual differences in the philosophy of science, with advice on such matters as avoiding pitfalls in collaborative work and preparing material for presentation along the way.

It is somewhat remarkable that an instructional booklet like this prepared for a primarily British audience is so applicable to graduate students in the United States. This provides some insight into the degree to which our scientific community is truly international with a high degree of comparability of standards.

I am pleased to recommend the book to anyone starting graduate work in the biological and medical sciences as well as to those who supervise graduate training.

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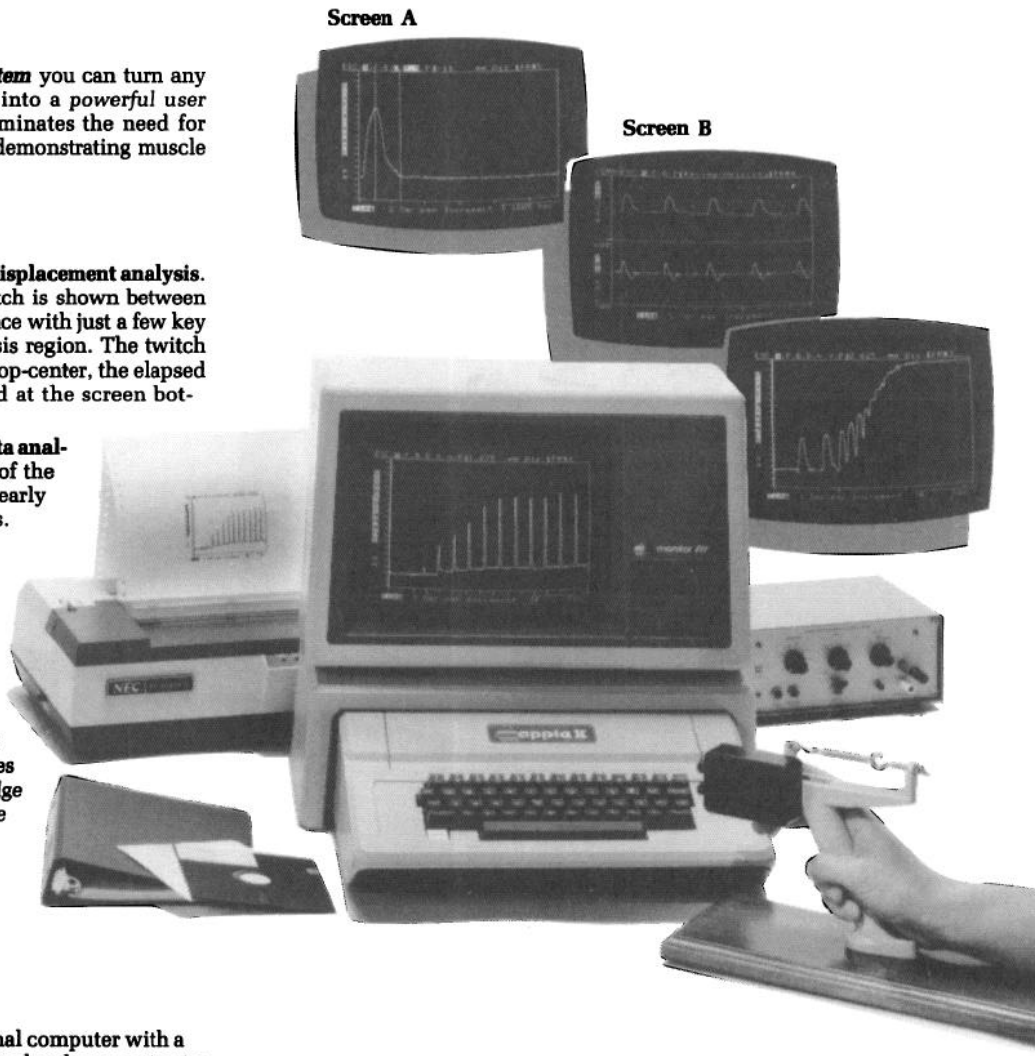

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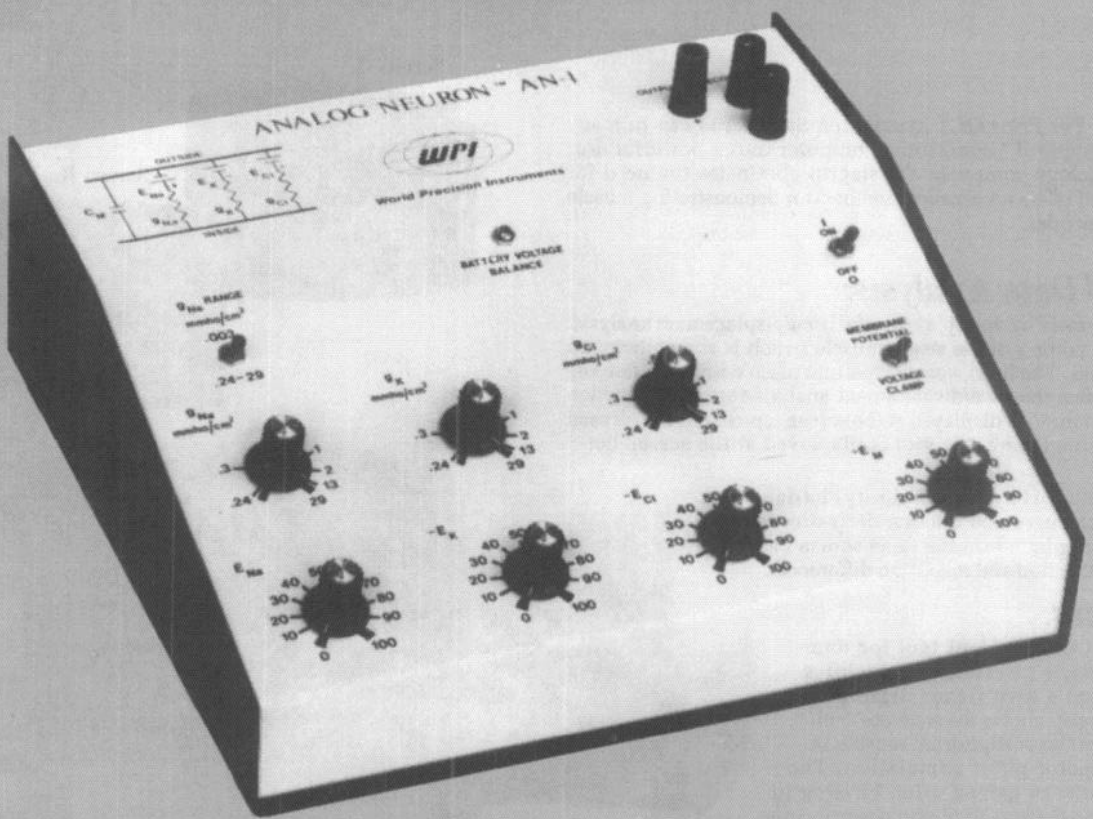

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