THE PHYSIOLOGIST

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Cover: Julius Hiram Comroe, Jr. (1911–1984), p. 3.

Next APS Executive Secretary-Treasurer

Martin Frank

Martin Frank has been selected as the next Executive Secretary-Treasurer of the American Physiological Society effective July 1, 1985.

Dr. Frank is presently the Executive Secretary of the Physiology Study Section, Division of Research Grants, National Institutes of Health, where he is responsible for the organization, coordination and management of the scientific merit evaluation of grant applications. In his capacity as the Executive Secretary, he has initiated workshops and symposia in emerging areas of physiology and has served as a spokesperson for NIH and the peer review process at universities and national conferences. In addition to his above responsibilities, Dr. Frank has pursued a self-initiated professional development program that enabled him to work closely with a number of senior administrators at NIH. One of his activities was the preparation of the application kit for Phase II of the Small Business Innovation Research (SBIR) Program which was mandated by PL 97-219, an amendment of the Small Business Act. Since December 1983, he has been a member of the Senior Executive Service Candidate Development Program sponsored by the Department of Health and Human Services, a highly competitive program designed to develop the Department's middle managers into its future leaders and executives. As a member of the program, he was on detail to the Office of the Assistant Secretary for Health, PHS, DHHS, where he worked with the Deputy Assistant Secretary for Health (Planning and Evaluation) focusing on FDA and CDC issues.

In 1973 Dr. Frank received his Ph.D. degree from the Department of Physiology and Biophysics, University of Illinois, Urbana, for research performed under the supervision of Dr. William W. Sleator on the excitation-contraction coupling mechanisms of cardiac muscle. In that year, he joined the Michigan Cancer Foundation, Detroit, as Research Associate with Dr. Samuel B. Horowitz, performing research on nucleocytoplasmic interactions in amphibian oocytes. In 1974, Dr. Frank became Research Associate in the Department of Pharmacology, Michigan State University, working with Drs. T. M. Brody and T. Akera on the effects of various pharmacological interventions on the E-C coupling mechanism in cardiac muscle.

In 1975, Dr. Frank joined the faculty of The George Washington University Medical School, Department of Physiology as Assistant Professor. His laboratory had an active research program supported by the American Heart Association, Nation's Capital Affiliate and by NIH. He taught muscle and cell physiology to medical and allied health students and introduced several courses for graduate students of Physiology. Since joining NIH in 1978, Dr. Frank has maintained an affiliation with GWU as an Associate Professorial Lecturer of Physiology. He has also served as a member of the Research Committee of the American Heart Association, Nation's Capital Affiliate, and is a member of the APS, Biophysical Society and the Society of General Physiologists.

Dr. Frank is a resident of Gaithersburg, Maryland, where he has been active in a number of community and city organizations. He is presently a member of the Gaithersburg City Planning Commission.

Editorial

Changes in Membership Profile of APS

In my Editorial in the December 1984 issue of *The Physiologist* 27(6): 383–384, I promised to expand in future issues on some of the matters mentioned. The first follow-up is inspired by an erratum. I intended to refer to a "meteoritic rise in the proportion of women members." The words came out in print "meteoritic use," which, fortunately, is somewhat meaningless.

Discovering this error led me to examine the basic data, which in turn led to discovery of several facts on changes in the Society's membership profile that may be of interest.

Seven years have elapsed since the APS began to provide for optional personal data on sex, age, and racial or ethnic origin on membership questionnaires, and during this period the total membership has increased 20%.

The Society membership has become somewhat younger on average, from 45% under 50 years of age to 50%.

The proportion of women members has risen from 6.5% to 11.0%.

White race representation has decreased 1%, from 93% to 92%.

Representation of minority groups have changed as follows:

	1978		1984	
	Number	Percent	Number	Percent
American Indian or Alaskan Native	6	0.2	7	0.15
Asian or Pacific Islander	146	4.2	239	5.2
Black	25	0.75	31	0.67
Hispanic	67	1.9	81	1.8
All minorities	244	6.9	358	7.7

The striking growth of the proportion of APS women members is clear. The word "meteoritic" may be a misplaced metaphor on more than one count.

Orr E. Reynolds
Executive Secretary-Treasurer

Julius Hiram Comroe, Jr. (1911–1984)

With the death of Julius Comroe on July 31, 1984, physiology lost one of its most effective scientists and teachers and medical science one of its most effective spokesmen. He contributed in important ways to the affairs of the American Physiological Society and the discipline that it represents and to the national effort in biomedical science.

Julius was born in York, Pennsylvania, in 1911, the son of a physician and a school teacher. He entered the University of Pennsylvania as an undergraduate in 1927 and, except for service in the Chemical Warfare Service (1944–46), remained associated with that University for 30 years. He received his BA in 1931, an MD in 1934, and served an internship at the Hospital of the University of Pennsylvania. He was then appointed an instructor in the Department of Pharmacology and remained there from 1936 to 1946, rising through the ranks until 1946, when he was appointed Professor and Chairman of the Department of Physiology and Pharmacology in the University of Pennsylvania Graduate School of Medicine, a position he held for 11 years. In 1957 he was persuaded to leave Penn to found and become the Director of the Cardiovascular Research Institute (CVRI) at the University of California, San Francisco (UCSF). In 1973 he gave up the directorship of the CVRI but continued as a professor of physiology, becoming emeritus in 1978. He remained active, however, until he became incapacitated by his painful terminal illness.

Starting in the late 1930's, Julius Comroe's earliest papers, dealing with the nature, location, and function of the chemoreceptors of the aortic arch and carotid body, earned him recognition as a leading contributor to the study of the physiology of respiration. For some 30 years he continued, with various collaborators and students, to make seminal contributions to the study of lung function in experimental animals and in humans.

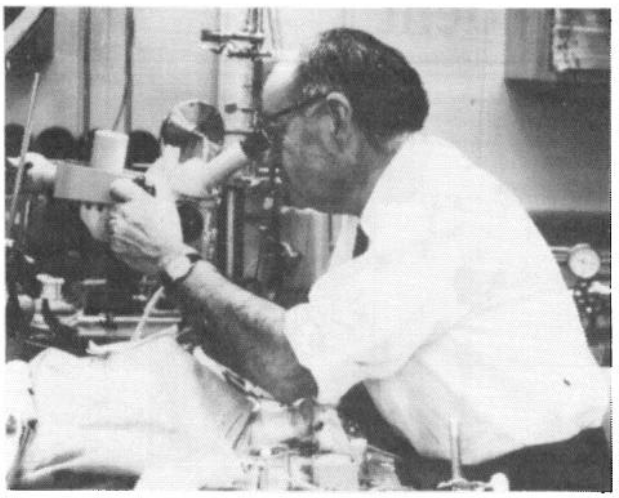
Julius Comroe, APS Fall Meeting, Columbus, OH, 1950

San Francisco TV representative interviewing Julius at the opening of the Cardiovascular Research Institute, 1958.

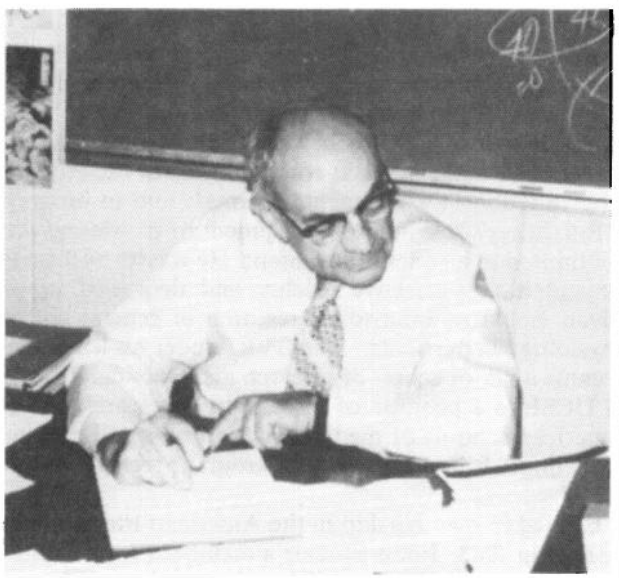
But Julius's role in the development of physiology was not limited to its scientific content. He was an enthusiastic and highly effective teacher and dedicated to the advancement of biomedical research in general and of physiology in particular. The CVRI under his leadership became a major center of research and training. The rise of UCSF to a position of leadership in research among American schools of medicine was in no small measure given impetus by Julius and the group he recruited to the CVRI.

Elected to membership in the American Physiological Society in 1943, Julius became a member of the Council in 1956, and served as president in 1960–61. His presidency was marked by the culmination of what has been referred to as "the Comroe revolution," which brought the end of the Board of Publication Trustees and the establishment of the Publication and Finance Committees.

Tensions had built up over a number of years between the Council of the Society and its Board of Publication Trustees (BPT) because of the rather striking difference between the substantial reserves of the Publication Fund controlled by the BPT and the minimal financial resources available to the Council in the Society's general fund. There may also have been an uneasy feeling on the part of some members that the BPT was often distracted from editorial policy by investment decisions. When the BPT was established in 1933, it had been given the function to consider and investigate matters pertaining to fiscal and editorial policies of the journals and to make recommendations to the Council for action. In 1946, however, largely to protect the publication funds from expenditure for purposes other than publication, no matter how worthy, the Constitution was revised to provide that the BPT was *invested with the full power of the Society* with regard to both editorial and financial policy of the publications. The BPT was required only to report its actions to the Council.



Julius in his laboratory dissecting a carotid sinus or body, early 1970s.



Julius working on his *Scientific Writing* course in the CVRI office after "final" retirement, 1977.

By the late 1950's the publication reserve fund was yielding in dividends and interest an amount that exceeded the annual operating costs of the Society, and the journals had a net operating income of about half that amount. None of these funds were available for the general purposes of the Society. These matters were the subject of repeated discussion at meetings of the Council. Finally at the Spring meeting of the Society in Atlantic City in 1961, an amendment to the Bylaws, previously distributed to the members, was offered. The amendment proposed abolition of the BPT and establishment in its place of a Publications Committee to deal with publications and editorial policy and a Finance Committee to be responsible for all the financial affairs of the Society. By the time President Julius Comroe was able to bring the matter to a vote by written ballot, the long and somewhat acrimonious discussion had carried the meeting to 6:30 P.M., and many of those originally present had drifted off. When the business meeting was reconvened two days later the result of the ballot was announced: the 74% in favor fell just short of the 75% required for a change of the Bylaws. On grounds that the previous vote had occurred after many members had felt constrained to leave the meeting, a move to reconsider was made by a member who had previously voted in the negative. In the new ballot, the amendment was supported by 78% of the 247 members present. It is of some interest that before the reconsideration ballot was achieved, Julius Comroe reluctantly declared out of order the motion of one member to reconsider on the grounds that he had previously voted on the losing side for the amendment. Both that member and the one whose motion to reconsider was found to be in order were later presidents of the Society.

Despite the fears that the reorganization would lead to raids on the publications funds, the reserves have remained intact, expended only for legitimate publications purposes, while the finances of the Society have remained stable—albeit with substantial increases in annual dues. The income from the Publications Fund investment has been useful from time to time to make up deficits in Society or Publications operations. Certainly the tensions between the Society and its publications function have disappeared.

Julius was elected to the National Academy of Sciences in 1961 and served as a member of the Board on Medicine established by the Academy in 1967. The Board was the precursor of the Institute of Medicine, which was established in 1970 with Julius Comroe as one of the founding members.

He served on numerous committees and advisory groups including the Board of Scientific Counselors (to the intramural program), National Heart Institute (1957–61), The National Advisory Mental Health Council (1958–62), The National Advisory Heart Council (1963–67) and, after the change of the name of the Heart Institute, the National Heart and Lung Advisory Council (1970–74) and the Advisory Committee to the Director of NIH (1975–78). He was the recipient of several honorary degrees and many honors and awards, including the award of the Association of Chairmen of Departments of Physiology for "outstanding contributions to the teaching of physiology" (1974), the Ray G. Daggs Award (1977), and the Jessie Stevenson Kovalenko Medal of the National Academy of Sciences (1976).

Following his retirement from the directorship of the CVRI he devoted himself to the historical analysis of the background of medical discoveries. A series of articles appearing in the *American Review of Respiratory Diseases,* under the title of "Retrospectroscope" were later gathered together in a book of the same title. In these essays, he explored the work that formed the necessary antecedents of medical advances, showing how many of these earlier pieces of essential information were derived from basic research, often in fields quite different from those in which they were eventually applied. The work makes an eloquent case for the importance of fundamental scientific work to the advancement of medical diagnosis and treatment.

Robert W. Berliner

People You Should Know

Doug Walgren . . .

Pennsylvania Congressman Discusses Alternative Methods, Statutory Guidelines for Animal Care, and the Role of Animal Care Committees

Doug Walgren is a fifth-term Democratic Congressman representing Pennsylvania's 18th Congressional District in the Pittsburgh area. Since 1981 he has served as Chairman of the Science and Technology Committee's Subcommittee on Science, Research, and Technology, which has Congressional responsibilities in the areas of science research and government-funded science programs and agencies, including the National Science Foundation. A strong supporter of broad-based science research, Mr. Walgren has been a Congressional leader in opposing the Reagan Administration's budget cuts in science research and education.

Mr. Walgren also serves on the Energy and Commerce Committee's Subcommittee on Health and Environment where he has supported health research efforts.

In October 1981 Mr. Walgren conducted public hearings to explore current practices in the use, care, and treatment of laboratory animals. Since that time Mr. Walgren has become a prominent Congressional spokesman for balanced legislation guiding the care and use of research animals and for the establishment of a federal program to develop alternative research methods.

In 1982 Mr. Walgren sponsored the "Humane Care and Development of Substitutes for Animals in Research Act," which died when the 97th Congress adjourned. In 1983, he introduced similar provisions as amendments which were incorporated in the "Health Research Extension Act," the authorizing legislation for the National Institutes of Health (NIH). These amendments were adopted by the 98th Congress, but the authorizing legislation was vetoed by President Reagan.

In looking ahead to the 99th Congress, the American Physiological Society asked Mr. Walgren these questions:

Congressman Walgren, what do you see to be the most important issue at this time regarding the care, use, and treatment of laboratory animals?

The most important issue, it seems to me, is to assure the public that the scientific community gives full consideration to humane treatment and care for animals that must be used in scientific and medical research. At the same time, we should be making a disciplined effort to develop new techniques to minimize the necessary use of animals in the future.

What specific legislative changes would you like to see the 99th Congress enact concerning laboratory animal practices?

I hope the 99th Congress, like the 98th Congress, will reenact the substance of amendments which were incorporated in the 1984 NIH reauthorization bill, but were lost when the bill was vetoed by the President. Three fundamental provisions should be approved: *1*) authorization of some funds for specific research in the development of alternative methods of research which can reduce the numbers of animals required; *2*) statutory recognition of the importance and authority for NIH guidelines on the care and treatment of animals in research funded by Federal sources; and, *3*) a requirement that all institutions carrying out research involving animals, sponsored or funded by the NIH, have animal care committees, including a veterinarian and a member without direct interest in the institution.

Why do you believe that these changes require an act of Congress rather than allowing for such changes to be made by a regulatory agency?

Minimal requirements in law are important to assure the public that certain standards will be followed and to give agencies clear guidance and support for their actions in this area. As the fundamental representative of the public, the Congress should set out the controlling principles whenever the basic values of our society are involved.

In your opinion, what have been the failings of Federal agencies in assuring enforcement of established criteria for the care, use, and treatment of laboratory animals?

Enforcement of standards of animal care and treatment are very difficult from the outside. Enforcement by government regulatory agencies is naturally resisted and resources to conduct inspections and review are insufficient. Instead of setting government agencies up as

outside enforcement agents, we should try to build an *internal* process that will assure continued attention and review of these kinds of concerns through institutional animal care committees.

At this time the only Federal legislative authority regulating animals is the Animal Welfare Act which empowers the US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) to enforce the approved standards for the care and treatment of laboratory animals. What is your assessment of APHIS as an enforcement agency and what steps would you like to see APHIS take to improve its role in this area?

The General Accounting Office is now doing a survey of the effectiveness of the enforcement of the Animal Welfare Act. I suspect they will confirm that there is essentially no significant effort able to be made on a nationwide basis by APHIS personnel. Testimony before our committee indicated that the attention of Department of Agriculture personnel was essentially consumed by problems of agricultural animal and plant concerns with little, if any, attention paid to laboratory animals used in other kinds of research.

Although your "Alternative Research Methods" bill (incorporated as an amendment to the "Health Research Extension Act" and passed by the Congress) was lost due to a Presidential veto, were you satisfied with what your bill would have accomplished if it had been enacted?

There are other proposals which I would support. But I think our amendment was especially good because it was the result of a process which responded to and took account of the concerns of all sides involved with laboratory animals. It reflects a consensus that all can support. It was especially good legislation because it was *reasonable* and *balanced.*

One of the provisions in your bill would have required NIH to design and implement a program to develop alternative methods. In your original version of the bill you sought for this purpose an authorization of $20 million for a three-year period, but in the final version of the bill the funding request was deleted. Where would the funds come from for NIH to implement this requirement?

Specific dollar authorizations were deleted for a variety of NIH activities covered in this bill because of Administration opposition and the fact that, as a practical matter, the NIH appropriations bill will control the specific level of effort that will be made. I understand that the opposition was not to the amount but the fact that a specific amount was established for a specific purpose. If our overall federal budget priorities were rearranged, there would be ample room for initiatives like this. Those who would do nothing in this area, in my view, miss the fact that new techniques could save us far more "research" money than the development of alternatives would cost, resulting in more, not less, money available for direct research.

Who Would You Like To Know?

Beginning with this issue of *The Physiologist* is a new feature entitled "People You Should Know." It is an activity of the Society's public affairs program and will feature in each issue an interview with a prominent individual who is of interest to physiologists.

For the inaugural interview Rep. Doug Walgren (D-PA) was selected because of his long-term efforts for legislation guiding the care and use of animal models and for the establishment of a Federal program to develop alternative methods.

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, CAE

What was your hope of accomplishment for a specific federal program to develop alternative methods?

NIH now invests several million dollars in research in this area. In view of the potential of nonanimal research method to reduce costs, I hope that a specific program authorized by Congress would underscore the importance and potential of this program, enabling it to compete on the merits with more entrenched, traditional program interests.

Your bill also would have established a second regulatory agency (NIH) for laboratory animal welfare, thus creating a likelihood that the standards of the Animal Welfare Act and the US Department of Health and Human Services (DHHS) guidelines could be somewhat conflicting and cause confusion for both the researchers and the animal care committee members as to which criteria must be followed. How would such differences be resolved?

There is no reason for a conflict. Regulations on laboratory animals set out in the NIH guidelines are generally consistent with the Animal Welfare Act, using the Act as a starting point to build a reasonable framework for its treatment of laboratory animals.

Two of your Congressional colleagues – Senator Robert Dole and Representative George Brown – sponsored bills that would have amended the authorities of the Animal Welfare Act instead of establishing a special authority for NIH to promulgate additional criteria for laboratory animal care and treatment. Is it your belief that the need for new laboratory animal legislation should be limited to only NIH/DHHS-funded programs rather than legislation that would apply to all research facilities covered by the Animal Welfare Act?

Amending the NIH bill was the first and best opportunity available to me to get through the entire legislative process provisions covering a substantial amount of federally funded research. Hopefully, these provisions could be a model for other legislation and agencies. I hope to work with Congressmen on other committees on uniform government-wide policies. Seventy-one percent of all research using animals is conducted by NIH, so NIH could set the standard in this area.

Both proposals to amend the Animal Welfare Act would have required all research facilities to establish instituional animal care committees, the same provision as you proposed in your bill. In your opinion, what are the most effective roles an institutional animal care committee can play in monitoring the care and treatment of laboratory animals?

It seems to me that properly working animal care committees are the best defense any institution has to prevent a scandal that would not only damage the institution but also would dangerously undermine public support for beneficial research. I also think there is a special potential in active animal care committees. In one stroke, they *1*) make a large, outside inspection enforcement system unnecessary; *2*) offer the best hope we have of doing the best we can for the treatment of animals in all the varying circumstances that arise which cannot be anticipated by legislation; and, *3*) can develop increased sensitivity whenever possible as new developments in research occur.

At the hearings conducted by Mr. Brown, the American Physiological Society proposed an amendment to the Animal Welfare Act that would make it a federal offense to break into and destroy and/or steal research records, equipment, and animals. Would you support such a measure as a means to help stem the rash of vandalism at many of the nation's research facilities?

YES.

Some of your colleagues in both the Senate and the House supported legislation that would have required an 18-month study of the laboratory animal welfare issues before any legislation would be enacted. What were your reasons for opposing that such a study be accomplished prior to the enactment of any new laboratory animal legislation?

The question of whether a study makes sense depends, in my view, on whether what is proposed to be done without the study is disruptive of present practices. In many ways, this legislation simply confirmed support

for what was already required by NIH (with respect to the "guidelines") or was already the policy of the more respected institutions in the area (with respect to animal care committees). The proposal to substitute a study is not unusual in Congress—and it usually reflects the effort of those who simply believe nothing should be done. But in my view, the rising hostility over animal research is pretty clear evidence that it makes sense to take steps now to assure the public that humane concerns are taken into account across the board.

From your experiences in gathering information about the care and treatment of laboratory animals, what do you believe to be the major failings, in general, of the nation's research facilities regarding animal welfare?

My effort was never intended to be a response to alleged abuses. It was intended to put in law some general principles and goals to guide agency-sponsored research and to assure the public, in the future, that their tax dollars and confidence in the research community are not misplaced.

What are your plans for laboratory animal legislation during the 99th Congress?

I will pursue whatever legislative opportunities are available to me and hope to work with other Members to promote this kind of legislation.

What role, if any, would you like to see the individual physiologists, and other scientists, of this nation play in efforts to improve the care and treatment of laboratory animals?

Congress welcomes suggestions from everyone who has a stake in this issue, particularly the medical and research community. Legislation is sounder when all who are interested have an opportunity to participate. It is the scientists, after all, who have day-to-day experience and can help develop legislation that is, in the end, truly effective.

I hope physiologists will take the lead in supportir every reasonable effort to improve the care and treatment of laboratory animals.

3 Lab Animal Bills May Be Reintroduced in 99th Congress

At least three of the legislative proposals involving the care and use of laboratory animals that the last Congress considered are expected to be reintroduced by their sponsors in the 99th Congress along with the possibility of an initiative seeking to ban the use of pound animals for the purposes of research and education.

The most likely laboratory animal bills to be reintroduced are:

Rep. Doug Walgren's "Alternative Research Methods."

Rep. George Brown's "Improved Standards for Laboratory Animals."

Rep. Robert Torricelli's "Information Dissemination and Research Accountability."

The Humane Society of the United States has announced its intentions of finding a sponsor to introduce a proposal that would make it a violation of federal law to release unclaimed pound animals for any reason other than pet adoption.

Of these four likely candidates for legislative consideration by the 99th Congress, the proposals by Walgren and Brown appear to have the best chance for passage during this Congress.

The last Congress did approve Walgren's proposals, which were incorporated in the bill to renew the legislative authorities of the National Institutes of Health. The bill was vetoed by the President but the Walgren amendments were not among the reasons cited by the President, who said that some of the amendments required excessive record keeping and other amendments made the bill too costly.

Brown's bill, introduced late in the second session of the 98th Congress, admittedly was a sounding board for developing a legislative proposal for consideration by this Congress.

Since 1981 Walgren has sought legislative reforms for the use of live animal models in research and has focused much of his attention in the areas of developing and utilizing alternative methods and on the local monitoring of laboratory animal care. His first bill, which failed to reach the House floor before the 97th Congress adjourned, covered a broad spectrum of requirements for all federally funded research. In the last Congress his bill was limited to animal research funded by NIH.

A question at this time is whether Walgren will again route a new proposal through the House Energy and Commerce Committee, where it could be added to the 1985 NIH renewal authorization bill and thus run the risk of another veto; or route it through the Science and Technology Committee where he is a senior member and the chairman of its Subcommittee on Science, Research, and Technology. Walgren's route selection undoubtedly will depend upon the scope and breadth of his new proposal.

Brown's proposed amendments to the Animal Welfare Act has gained support from scientific communities since its introduction last fall. By and large, the major opposition to the bill comes from the US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) which has traditionally resisted any additional requirements placed upon it through the Animal Welfare Act.

The scientific community's support for the bill is largely based upon Brown's consideration to include an amendment that would make it a federal offense to break into any federally funded research institution and steal or destroy research records, equipment, or animals. The amendment, proposed by APS during public hearings on the bill last September, has been endorsed by several national research/education groups including the American Psychological Association and the Association of American Medical Colleges.

The one common point between the Brown and Walgren bills is the requirement to establish institutional animal care committees to monitor the treatment of laboratory animals with the only difference being that the Brown bill requires APHIS inspectors to review all Committee reports during APHIS inspection. This was an APS recommendation.

The Brown bill also adds an additional standard for providing adequate exercise for laboratory animals and would establish a national clearinghouse for the exchange of research information.

The Torricelli bill also would provide a national clearinghouse for research information in addition to creating a 20-member, Presidential-appointed agency within the National Library of Medicine for the purpose of reviewing all approved-for-funding grants involving the use of animals. Those grants found to be duplicative of other grants-in-progress or research already completed would be vetoed for funding.

The proposal sponsored by Torricelli was initiated by United Action for Animals and introduced last year without input from the scientific community. However, the proposal for this Congress is expected to be somewhat modified and display some of the concerns of the scientific community including deletion of the implied veto power by the 20-member agency on those grants approved-for-funding by accepted peer-review standards.

Whereas the United Action for Animals has found a sponsor for its proposed legislation, the Humane Society of the United States is looking for a sponsor. The Society is proposing that federal animal control laws include a provision that would make it illegal to release any unclaimed pound animal to institutions for use in research or educational programs.

The Humane Society's director for laboratory animal welfare, Dr. John McArdle, has said that the Society's primary goal at this time is to put an end to all pound release of animals except for the purpose of pet adoption. The Society has been concentrating its efforts at the state and local levels but is now opening another front at the federal level. McArdle has predicted that pound release of animals will be halted nationally before 1990.

William M. Samuels, CAE

The Rat in Biomedical Research

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The rat is a major experimental animal in the fields of transplantation, immunology, basic genetics, reproduction, cancer, behavior, aging, toxicology, biochemistry, and physiology. It is also of worldwide economic and medical importance, since it destroys one-fifth of the world's crops each year, carries many diseases to mankind, and even attacks humans. An article in the *National Geographic* (9), entitled "The rat—lapdog of the devil," describes both the tremendous impact of the destructive activities of this animal and the major contributions that it has made to human health as a laboratory animal. It concludes that the rat is one of the most important animals with which man must interact.

The strain of rats that has been used most for experimental work is the Norway rat (*Rattus norvegicus*), and its early history has been documented by Robinson (89). Its origin is thought to have been in the region between the Caspian Sea and Tobolsk and extending as far east as Lake Baikal in Siberia. It spread with the development of commerce and reached Europe and the United States in the 18th Century. At the beginning of the 19th Century, a number of wild rats were trapped for the sport of rat baiting, and it is from these rather gruesome origins that domesticated strains of rat were developed.

In the middle of the 19th Century, the rat was used for studies in nutrition, physiology, and anatomy. The research animals in the United States were thought to have originated in Europe and then spread back to Europe and the Far East. The first inbred lines of rats were developed at the beginning of the 20th Century by Donaldson and his colleagues and by Castle and his colleagues. The first studies were in basic genetics, investigating the segregation of coat color, and in cancer. The development of inbred strains for use in these experiments did not progress very rapidly, and it was not until the work of Owen and his colleagues at the California Institute of Technology, Palm and her colleagues in Philadelphia, Stark and his colleagues in Prague, Gill and his colleagues in Pittsburgh, and Aizawa and his colleagues in Japan that the immunogenetics of the rat was systematically studied and many of its genetic parameters were defined (26, 38, 105). Recently, compilations of basic data on the rat (3, 17), studies of its ecology (8), and the rationale for its use as an experimental animal (25) and as a model for various human diseases (4, 5, 16) have become available. Developments in basic genetics and in models of disease are regularly updated in publications of the Workshops on Alloantigenic Systems of the Rat published in *Transplantation Proceedings* (27, 30–32), the *Rat Newsletter* published by the Department of Pathology at the University of Pittsburgh, and *Animal Models of Disease* published by the Registry of Comparative Pathology.

Aging

The rat is a major animal for aging studies, especially the F344 strain. An important aspect of aging studies is to follow the development of lesions with time and the size of the rat; the availability of inbred strains and the considerable background work done in physiology and biochemistry make this an ideal experimental animal for these studies. Inbred and randomly bred strains of rats show major, spontaneously developing, age-related lesions in the kidney and heart and in the nervous, skeletal, muscular, vascular, endocrine, and immune systems (5). In the kidney, the major lesions are chronic nephritides of various types, including glomerulonephritis and glomerulosclerosis (7); some strains of rats spontaneously develop kidney stones. The major defects in the heart are myocardial degeneration and fibrosis. In some cases, thrombotic lesions and endocardial and subendocardial proliferative lesions are also seen. In the nervous system, the most common disease is spinal nerve root degeneration. Occasionally, spontaneous degeneration of the retina is also observed. Degeneration of the skeletal muscle, especially in the heart and limbs, has been observed in both inbred and randomly bred strains of animals. This lesion can be associated with motor end-plate degeneration. Attempts to inbreed these animals, so that the genes controlling the muscle degeneration can be isolated, have not been successful. Osteoarthritis, chronic spondylitis, and aseptic necrosis of the bone have also been observed. Polyarteritis nodosa is the most common vascular lesion seen with aging in the rat. Arteriosclerosis in the aorta, coronary and major cerebral blood vessels also occur. On occasion, spontaneous hypertension develops in various inbred and randomly bred strains of rats other than those specifically developed to be hypertensive (see below). In the endocrine system, the most important lesions are adenomas of the adrenal medulla, parafollicular (C) cells, anterior pituitary, and pancreatic islet cells. Immunologic functions also change with age. The immune response to antigens decreases after five years of age in both males and females, and this decrease is genetically influenced (60). There is an increase in T-lymphocyte cell reactivity which may play a role in the development of autoimmune disease with aging (63). Finally, there is an increase in spontaneous tumors in the rat with age (15).

The development of age-associated lesions can be influenced in many cases by the animals' diet. Excessive feeding leads to obesity and an acceleration of age-associated lesions. By contrast, restricted calorie intake can decrease the incidence of such lesions.

Autoimmune Diseases

Autoimmune diseases occasionally occur spontaneously in the rat, but the major use of the rat in this field is in the study of induced autoimmune disease. The major diseases studied are five: experimental allergic encephalomyelitis (EAE), thyroiditis, arthritis, myasthenia gravis, and renal disease.

EAE (103) is a well-studied model for the demyelinating diseases of the central nervous system, and the rat is the major experimental animal for studying this disease. EAE is produced by the injection of encephalitogenic protein with or without complete Freund's adjuvant. A hyperacute form of the disease can be induced by incorporating *Bordetella pertussis* into the immunizing mixture or by immunizing with a crude extract of the central nervous system plus *B. pertussis*. The central nervous system extract or the encephalitogenic protein may be prepared from the brain and spinal cord of a variety of species, but the guinea pig is the most common source. The clinical signs of the disease wax and wane, and the pathological process can spontaneously remit or progress to permanent paralysis and death. The disease is transferred by lymphocytes, and susceptibility to it is controlled by a polygenic mechanism involving both a gene linked to the major histocompatibility complex (20) and non-MHC genes (19).

Thyroiditis (5, 82, 103) occasionally occurs spontaneously in the BUF strain and can be induced by immunization with syngencic or allogeneic thyroglobulin in complete Freund's adjuvant. The intensity of the disease can be enhanced by incorporating *B. pertussis* vaccine into the immunization mixture. The inbred strains have different susceptibilities ranging from a high incidence of the disease (RTI^c) to complete resistance (RTI^u). The pathological effects can be transferred by lymphocytes.

The rat is an important animal for the study of the pathogenesis of arthritis. The major model is induction by the intradermal injection of killed *Mycobacteria tuberculosis* in complete Freund's adjuvant (adjuvant arthritis), and there is variation in susceptibility to the development of arthritis among different strains of rats (95). This form of arthritis has many features of the human disease and is mediated by T-lymphocytes (45). Another type of autoimmune arthritis can be produced by immunization with type II collagen, which is a component of joint cartilage, and this form of arthritis is associated with both cell-mediated and humoral immunity to the type II collagen (45). Immunity to type II collagen has also been observed in adjuvant arthritis and in human rheumatoid arthritis.

An excellent model for myasthenia gravis has been developed in LEW rats by inducing an autoimmune response to the acetylcholine receptors purified from the electric organs of electric eels, from torpedos or with the acetylcholine receptors purified from normal LEW rat muscle or fetal calf muscle (68). The conformationally intact acetylcholine receptor molecule is important, since denaturation greatly reduced its immunogenicity. The disease is caused by the binding of antibodies to the acetylcholine receptors of the motor end plates of the nerve, and this causes a net reduction in the number of muscle acetylcholine receptors. The antibodies from the immunized animals can cause the autoimmune disease in normal rats by binding to the muscle acetylcholine receptors and decreasing their number. The major clinical sign of the disease in the rat is weakness, and there is electromyographic evidence of impaired neuromuscular transmission. After the passive transfer of antibody, the clinical and physiological changes of myasthenia gravis are observed within 24 hours.

Two kinds of immunologically mediated renal disease have been studied in the rat: immune complex disease (96) and antitubular basement membrane disease (74). Kidney transplantation between rat strains identical for the MHC antigens, but different for non-MHC antigens, is followed by immune complex (membranous) glomerulonephritis. The recipients developed circulating immune complexes and circulating antibodies against the allogeneic tubular epithelial antigen. Inbred strains of rats differ widely in their susceptibility to interstitial nephritis induced by rabbit renal tubular basement membrane preparations, and susceptibility is determined partly by MHC-linked genes. The disease is characterized by antitubular basement membrane antibodies, monocytes, natural killer cells, and sensitized T-effector cells. The primary mediator of the disease is not yet identified, since passive transfer of antibody may or may not produce lesions, and immune cells placed under the kidney capsule induce only minimal disease.

Basic Genetics

In recent years, the studies on rat genetics have rapidly defined many aspects of the structure and function of the major histocompatibility complex (26), and a number of issues concerning the polymorphism of MHC and non-MHC genes (26, 27, 30–32). Studies on the serologically active loci in the MHC have shown that there is a low-level polymorphism: 12 class I antigens and 9 class II antigens have been defined. The *RT1.A* and *RT1.E* loci define the conventional limits of the MHC, and the *RT1.C* locus appears to be located in a position comparable to that of the *Qa* and *Tla* loci in the mouse. Other *Qa/Tla*-like antigens have also been identified, but they have not as yet been mapped to the MHC. The expression of class I antigens varies between lymphocytes and erythrocytes and among strains. The *RT1.E* antigen is detectable on the surface of BI-lymphocytes, but not erythrocytes, and its expression is controlled by a gene that maps near *RT1.A*. There are multiple class I loci in the MHC, as identified by monoclonal antibodies reacting with their products, but many of them have not yet been mapped. The class II loci of the rat, *RT1.B* and *RT1.D*, are comparable to the *I-A* and *I-E* loci of the mouse, both in terms of their functions and the biochemistry of their products. The loci coding for class II molecules are associated with strong mixed lymphocyte reactivity responses and immune responses to synthetic and natural antigens. The rat also has an *Ss*-like protein, but its location has not been mapped. The organization of the loci in the MHC of the rat is like that of the mouse and different from humans and other species that have been studied. Thus it appears that in the course of evolution an inversion occurred in the prototypic Muridae which put the class II loci between the two major class I loci.

Loci controlling enzymes and loci influencing reproduction are linked to the MHC. Glyoxalase I is present, as in the human and the mouse, and its map distance from the nearest class I locus is approximately the same

as in the human. The gene controlling neuraminidase is present, as in the mouse, on the opposite side of the MHC from glyoxalase. The growth and reproduction complex (*grc*) contains at least two recessive genes: *dw-3,* which causes small body size in both males and females, and *ft,* which causes male sterility with an arrest at the primary spermatocyte stage of sperm development and decreased reproductive capacity in females due to a defect in the maturation of the primary ovarian follicle. The *grc* is comparable to the mouse *t* semilethal alleles: it acts at an early stage of meiotic prophase I, causes reduced testicular weight, causes sterility due to lack of sperm production, and is not associated with any known chromosomal or hormonal abnormalities.

Studies of the polymorphism of MHC antigens have shown that, in natural populations of rats, there is significantly less genetic variation compared with that of the mouse. A high proportion of the class I and II antigens detected in wild animals are structurally and functionally indistinguishable from those in the inbred strains, suggesting that extensive polymorphism is not required for the effective functioning of the MHC of the rat. In addition to the restricted polymorphism, there is also a high degree of linkage disequilibrium between loci within the MHC. In one population of wild rats, this linkage disequilibrium was as high as was theoretically possible given the individual gene frequencies found in the population.

A variety of biological functions are controlled by genes in the MHC of the rat, and some of these functions have recently been assigned to specific loci. The genetic control of the immune response in the rat is a complex polygenic mechanism involving both MHC and non-MHC genes and a sex influence such that females have a higher and more heterogeneous antibody response than males. The role of class II antigens in the control of immune responsiveness in the rat is important, as in the mouse, and the immune responsiveness can be inhibited in vitro with anti-class II antibodies. Cell-to-cell interactions manifest themselves in mixed lymphocyte reactivity, graft-vs.-host reactivity and cell-mediated lympholysis. They are all controlled by genes in the major histocompatibility complex. The major stimulus for the mixed lymphocyte reaction is provided by antigens coded by the class II loci, and a minor stimulus may also be provided by antigens encoded by *RT1.A*. The graft-vs.-host reaction is also directed against class II antigens. By contrast, the major stimulus for cell-mediated lympholysis is provided by class I antigens, with the possibility of a relatively minor stimulus being provided by non-MHC antigens. As discussed in the section on transplantation, the rat has been used extensively to define the role of MHC and non-MHC antigens in organ rejection. The development of several strains of nude rats (Rowett and New Zealand) has provided an excellent vehicle for the study of tumor growth (16) and for the growth of antibody-producing hybridomas (75). The large size of these animals provides ample amounts of material for study, and repeated tapping of the ascites fluid provides large quantities of antibody from each animal.

Cancer

Inbred and randomly bred rats are susceptible to the development of spontaneous, virally induced, and chemically induced tumors in all organ systems (5). They can also serve as excellent hosts for transplanted tumors in studies using this approach. The most common strains in which spontaneous tumors have been found are the ACI, WF, BN, and F344 strains. Extensive studies of virally induced tumors have been performed using the WF and BN strains. The rat has been the major animal used in toxicology for screening carcinogenic compounds. It provides all of the different types of animals that can be used in these studies: randomly bred, outbred, inbred, and congenic (25). Such animals must be carefully selected for the characteristics necessary for the experiments contemplated. This choice is critical, because a great deal of important information can be lost or great cost and effort can be expended for no useful information if the inappropriate animal model is chosen.

There are four major types of rats available for use in biomedical research, and each has its specific applicability. First, randomly bred rats can be derived either from colonies or from wild populations. They are particularly useful for first-level chemical screening, a source of mutants, and starting material for inbred lines. Second, specifically structured outbred populations can provide a stabilized gene pool that is useful for first- and second-level screening procedures. Third, inbred strains and F_1 hybrids are useful for studying individual traits in a population, answering specific experimental questions or comparing results over a long period of time, and detailed genetic analysis. Fourth, congenic strains are useful for studying the effects of specific genes and their alleles on a common background. The large variety of rat resources now available (17, *Rat Newsletter*) provide a rich source of material for all of these types of studies.

The genetic control of the immune response to cancer has been studied extensively in virally induced cancers (48) and in transplanted tumors (2). Some strains are susceptible to induction of these tumors and others are resistant. Genetic segregation studies, measurement of tumor growth, production of tumor products, etc., have been done to establish the genetic basis of resistance and susceptibility. The study of the intracerebral and subcutaneous growth of a transplantable gliosarcoma showed that susceptibility is transmitted as a dominant trait and that at least two genes or gene complexes are involved —one linked to the major histocompatibility complex and one segregating independently of it (2). The genetic mechanisms involved did not appear to be affected significantly by the site (environment) in which the tumors grew. The antibody response consisted of antibodies to the histocompatibility antigens of the tumor and to tumor-associated antigens. The antibody response to the tumor-associated antigens was correlated with tumor regression. Thus the studies in rats showed that tumor susceptibility is under polygenic control and one of the major genes influencing the responses linked to the major histocompatibility complex.

Diabetes

The rat provides models for both diabetes mellitus and diabetes insipidis. The best model available for the study of spontaneous insulin-dependent (juvenile onset) diabetes mellitus in humans is the BB rat (5). This is not an inbred strain, but the evidence to date strongly suggests that complex genetic factors are involved in the etiology of diabetes. Recently, some evidence has been provided for the linkage of a major predisposing factor to the MHC (12, 40). Both males and females are af-

fected, and the mean age of onset is 90 days, as determined by glycosuria and/or an abnormal glucose tolerance test. The onset of overt diabetes is usually rapid. Its manifestations range from modest abnormalities in glucose metabolism (chemical diabetes) to fully developed diabetes mellitus, and some of the animals can have spontaneous remission of their diabetes. The overt clinical syndrome consists of hyperglycemia, hypoinsulinemia, ketosis, polyuria, glycosuria, and weight loss.

The pathology shows a selective destruction of the β-cells of the islets of Langerhans by an inflammatory reaction (insulitis), and the degree of destruction correlates with the severity of ketosis. The immunologic basis for this lesion has been shown by three lines of evidence: *1*) prevention or reversal of the diabetes may be achieved by antisera to rat lymphocytes (67), transfusion of whole blood from normal animals (90), induction of immunologic tolerance with bone marrow from normal animals (72), and neonatal thymectomy (66); *2*) the passive transfer of concanavalin A-treated splenic lymphocytes from acutely diabetic rats can induce the disease (57); and *3*) there is a decreased number of T-lymphocytes (14, 40).

The Brattleboro rat has hereditary hypothalamic diabetes insipidis associated with high plasma renin activity, high angiotensin II concentration, and spontaneous hypertension (11). These rats lack angiotensin II-binding sites in the neurohypophysis and have a high level of activity of angiotensin-coverting enzyme, which can be reversed by vasopressin therapy (11). They also have defects in lipogenesis (43).

Cardiovascular

Rats have been used for the study of cardiovascular phenomena such as the effects of drugs on the vascular system, air emboli and decompression sickness, and the protective effects of drugs and decompression chambers. The use of these animals in physiological studies has been valuable in developing ways to prevent or treat decompression sickness and the disastrous effects of air emboli, one of the occupational hazards in deep sea diving. These same physiological preparations have been used in studies of hypothermia as encountered in severe exposure to frigid environments, e.g., in space travel (86, 87).

Hypertension

The two most important strains of animals used for hypertension research are the spontaneously hypertensive (SHR) strain and its two substrains, stroke-prone and obese, and the Dahl salt-resistant (R) and salt-sensitive (S) strains. The SHR strain (5, 77, 93) is the most important in hypertension research, because it is a good model for essential hypertension in humans: the rats sponteneously develop hypertension, which increases with age; the hypertension is more severe in males and leads to cerebral, myocardial, vascular, and renal lesions; and blood pressure is responsive to control by antihypertensive agents. The hypertension is a genetically transmitted trait and is most likely polygenic. In well-maintained colonies, 100% of the animals develop hypertension between 5 and 10 weeks of age. It is important, however, to evaluate the particular group of animals being used, since the SHR strain is maintained in many places where genetic monitoring is not strict, and some studies have shown that animals from different sources can be heterozygous (29). The Wistar-Kyoto (WKY) strain has been used as the normotensive control for the SHR strain, but the WKY strain is not genetically well defined and its validity as a control strain is questionable.

The stroke-prone substrain of SHR (78) was developed by selecting animals from litters in which there was a high incidence of cerebral hemorrhage. Sixty to eighty percent of the animals in this substrain develop cerebral hemorrhages by 5 months of age. The obese substrain of SHR (58, 59) was selected by breeding heterozygotes from litters in which some of the animals were obese. Twenty-five percent of the offspring of these animals are obese, and it appears as if obesity is an autosomal recessive trait. The obese animals have increased food consumption, deposition of excessive body fat, increased numbers of atherosclerotic plaques in the aorta and other vessels, hyperlipemia, and increased serum cholesterol.

Two lines of Dahl rats were developed by selective inbreeding (56, 88). One is resistant (R) and the other is sensitive (S) to the development of hypertension when given a high (8%) salt diet. This trait involves genetic factors, most likely polygenic, but the lines do not breed true and they must be maintained by continued selection for or against salt-induced hypertension.

Infection

The rat has been used extensively for the study of infectious diseases caused by bacteria, fungi, mycoplasma, rickettsia, viruses, and parasites (5). Many of these diseases have been well characterized in the rat, and this animal serves as an important model for studying the pathogenesis of the diseases. The experimental models that have been studied in greatest detail are those involving infection with *Nippostrongylus brasiliensis* (76, 102), *Schistosoma mansoni* (83), and *Listeria monocytogenes* (49, 50).

A long series of experiments using *Listeria* was able to show that there are different genetic factors restricting antigen-induced proliferation in vitro and delayed-type hypersensitivity to various *Listeria* antigens and antimicrobial resistance to live *Listeria* organisms. The MHC loci acting as restricting elements are different in each case, and the requirements for eliciting cellular resistance to microbial infection appear to be different in the rat from those in the mouse. The major restricting element in the rat is controlled by a class I locus, whereas in the mouse it was reported to be a class II locus. Subsequent studies in the rat and reexamination of the question in the mouse have confirmed the conclusions from the work in the rat. This finding illustrates the importance of examining more than one species when studying biological mechanisms. The work in the rat which gave results different from those in the mouse led to a reassessment of the situation of the mouse and revision of the original conclusions drawn from the work in that species.

Reproductive Biology

The rat has been used predominantly in studies of reproductive endocrinology and of the morphology and

control of the menstrual cycle. This physiological work laid the foundation for much of our understanding of these processes in mammals and has become a part of the standard endocrinological and physiological literature. In recent years, the rat has been used extensively to study the immunologic interplay between the mother and the fetus and to investigate the genes that regulate development (24, 36). The immune response to the paternal component of the placental antigens is directed against a class I antigen that is not one of the classically identified transplantation antigens (22). Monoclonal antibodies have been raised against this antigen using spleen cells from pregnant females without any other form of immunization (23). This approach promises to give new insights into the nature of the immunologic relationship between mother and fetus and the reason that the fetus is not rejected.

A long series of studies in rats (13, 33, 34) showed that immunization of pregnant females could alter the immune responses of their offspring. This process is genetically controlled, such that immunization of a low-responder strain enhances the immune response of the offspring, whereas immunization of a highly responding strain depresses the immune response of the offspring. The reason for these findings is the transfer of antigen across the placenta and the subsequent stimulation of the developing lymphoid system of the fetus. These studies were extended to humans (35), and immunization of pregnant women with tetanus toxoid was shown to sensitize their offspring so that they were born producing an immunoglobulin M antibody, responded more rapidly and with a large amount of antibody to the routine series of DPT injections in the neonatal period, and had a higher level of immunity to tetanus in the second year of life than those children whose mothers had not been immunized. This sequence of studies demonstrated clearly how a basic phenomenon discovered in rats could be elucidated immunologically, biochemically, and genetically and then the information transferred to clinical practice with the potential for developing new approaches to mass immunization.

A variety of size and fertility defects has been observed in the rat (28), and the best-defined ones are those controlled by the growth and reproduction complex (*grc*) (28, 61, 62), the *Tfm* syndrome (6), and the genes restricting hood pattern and affecting fertility, the H^{re} genes (37). The *grc* is the analogue in the rat of the *t* haplotypes of the mouse, and it is discussed in detail under basic genetics. In brief, it contains genes causing small body size (*dw-3*) and fertility defects (*ft*): males are sterile due to an arrest of spermatogenesis at the primary spermatocyte stage, and females have a reduced reproductive capacity due to rapid aging of the ova. Recent studies (36) provide evidence for such genes in humans and substantiate further the generality of this phenomenon.

The testicular feminizing syndrome (*Tfm*) has been discovered in several species, and considerable work has been done on the form present in the rat. This syndrome is transmitted by females to one-half of their male offspring in a pattern consistent with either a sex-limited autosomal dominant gene or an X-recessive gene. These animals cannot respond to androgens in utero; hence, tissues such as the prostate, Wolffian duct derivatives, and external genitalia do not differentiate. The *Tfm* animals develop as male pseudohermaphrodites.

The H^{re} gene is a dominant gene which causes restriction of the colored area of the body in the hooded Irish and self-color patterns. Males carrying this gene have testicular tubular dysgenesis, which leads to sterility and a slightly reduced growth rate. The cause of this sterility is a relative insensitivity of the germinal epithelium to follicle-stimulating hormone. This gene is not linked to the MHC and is different from the genes of *grc*.

Transplantation

The rat is the major animal used in organ transplantation studies, and many of the advances in understanding the immunologic mechanisms involved in tissue rejection have come from studies in this species (3, 26). The size of the rat makes surgical procedures feasible, provides large amounts of cells and serum on a regular basis, and allows serial biopsy of the transplanted organs to assess the rejection process. Previously, the only drawback to the use of the rat was the relatively modest amount of knowledge about its genetics, especially the structure and function of its MHC, that precluded a serious genetic approach to the immunologic problems of transplantation. This has now changed because of the recent work in the genetics of the rat, especially in the definition of the structure and function of its MHC (26). Also, a large number of congenic and recombinant strains have been developed by various investigators, and reliable inbred strains are now available; therefore, the genetic resources for a sophisticated immunologic approach to the problems of transplantation using the rat are now available.

The rejection times of various organs in different strain combinations are summarized in Altman and Katz (3), and a summary of the different MHC loci involved in organ rejection is given in Gill et al. (26). The general strategy in these studies was to employ combinations of inbred, congenic, and recombinant rats to study the relative roles in the rejection process of MHC and non-MHC antigens and to identify the roles in graft rejection of the antigens encoded by various loci within the MHC. Such transplantation studies have been done using skin (38, 54), kidney (80, 81, 97), heart (39, 41, 53, 54), bone marrow (85, 101), liver (51), and pancreas (55, 73). Transplantation in the brain showed that fetal brain transplants can reduce cognitive deficits in rats with frontal cortex lesions (64) and that dissociated cell suspensions prepared from the substantia nigra and septal regions of rat embryos can be grafted into the caudate-putamen and hippocampus to improve motor impairment in aged rats (18). These experiments hold particular promise for the treatment of consequences of aging such as Parkinson's disease.

A number of studies have been performed in rats to investigate the nature of the immune response in privileged sites, such as the anterior chamber of the eye (52, 94) and the brain (21); the various strategies by which cells and passively administered antibodies can enhance graft survival (10, 65), and the effects of cyclosporine in prolonging grafts (46, 70, 84, 98, 100). Recently, the effects of cyclosporine have been shown to be under genetic control (84).

Behavioral Science

Next to reproducing the phenomena under study the most important factor in choice of an animal model is

the extent of existing knowledge about the animal. A century after it was first used for research more was known about the rat than about any other infrahuman species (14a, 104). For this reason the rat has continued to be the animal of preference in many fields of investigation and particularly in behavioral studies. The very first use of the white rat for research was by Stewart in 1895 for studies of effects of alcohol and diet on behavior. Stewart changed from grey rats to white rats in the belief that the albino would prove more tractable in handling, thereby propagating the widely held false belief that tameness is an effect of the albino gene. Stewart influenced Donaldson, then at the University of Chicago, to use white rats. These animals were immediately put to use by the Chicago Psychology Department in major lines of research on the relationship of organic processes to mental processes. This work was of fundamental importance because apparent differences in psychological processes between humans and animals were considered the primary evidence against evolutionary theory and therefore against the view that study of animal biology could have relevance for human biology. It is for this reason that the bibliography of Donaldson's *The Rat* included psychological literature, although ostensibly the book was concerned with anatomy and physiology. Of the Chicago group of rat investigators, Watson is the one best remembered today. From his research his 1914 book, *Behavior: An Introduction to Comparative Psychology,* established behavioral science as an alternative to mental science, providing a conceptual framework within which the study of humans could be related to the study of infrahumans. The showing of biological commonality of rat and man in psychological functions resolved the man-animal difference controversy and justified animal models as a general approach to biomedical research.

It was Bertrand Russell who first pointed out that scientists who observed animals in nature drew the conclusion that life patterns were fixed, whereas those who experimented with animals in the laboratory concluded that environmental factors were important. The discovery that it was even possible to intervene in biological processes such as disease came from 20th Century animal experimentation. We take it so much for granted that we do not realize that the very idea of human intervention for health is a result of animal experimentation.

Much of the advance in medicine since World War II has stemmed from the biochemical knowledge built on the Watson-Crick analysis of the Mendelian genetic coding mechanism. Only historians of science also recall that the applicability of Mendelian genetics to humans was still a matter of controversy in the pages of *Nature* during World War II. Fisher's 1918 paper on Mendelian inheritance generated the most controversy of any paper in the history of science. He demonstrated that if inheritance were Mendelian, then one could not infer the genetic structure from naturalistic study, but only from genetic experiments. Since one cannot carry out genetic experiments on humans, it follows that animal experiments are the only available route.

Castle used rats in the experiment that first proved Mendelian inheritance in animals. Had we followed the alternative genetic theory, apparently supported by studies on humans, we might never have entered the modern era of biochemistry.

Shortly after the turn of the century, the Wistar group (47) performed surgery on rats at different stages of pregnancy. They learned that effects of surgery vary with embryonic age. Much of our knowledge of fetal risks and approaches to surgery for pregnant mothers stems from that research. That research also revealed for the first time the possibility of treatment of fetal conditions, an idea now bearing fruit in prenatal intervention for prevention of birth defects.

Small (92) introduced maze experimentation with rats. At Cattell's suggestion, Thorndike extended this work to humans, establishing the field of educational and psychological measurement whose immediate health impact was to provide means for differential diagnosis and special education. Thus it was the rat experiments that pointed toward differentiating mental deficiency from emotional and other problems.

Maze experiments became a major research vehicle for the study of learning. The entire theme of environmental modification of behavior was motivated by rat experiments, first in physical pattern mazes and later in the temporal pattern problems of operant chambers (91). The vernacular phrase, "a learning experience," reflects an orientation motivated primarily by rat experimentation. Only someone who has had the heartbreaking experience of working in an institution for disturbed children in the first half of the century can appreciate the miraculous gains from behavioral therapies. Thorndike's discovery of the role of action in learning in rats influenced not only educational methods but also initiated a turn toward active postoperative therapies to speed recovery.

Lashley explored the behavioral effects of extirpation of precise areas of the brain in rats. His findings demonstrated that brain functions were not inevitably lost. This evidence encouraged neurosurgery and attendant neurosurgical advances for cases previously deemed hopeless.

The use of cortical implants for electrical and chemical stimulation of brain areas to activate specific processes originated with cats and with rats (71) as a logical next step to extirpation of those areas. The techniques themselves have led to research on neural stimulation implants for human as a means of overcoming certain neurological spastic or otherwise uncontrollable movements.

Olds and Milner (79) found that rats will self-stimulate certain areas of the brain via cortical implants. The research is of particular interest because the results were totally unexpected and were part of a revolution in our understanding of mental functions. An active brain was considered an anatomical impossibility until the development of new staining techniques in the 1940's revealed more neural connections. An active brain was considered a functional impossibility until continuing brain action was found in surgically isolated brain sections in the 1950's. Three or four years before these findings, a proposal was made at a conference in Boston that animal experiments in psychology be replaced with simulations, and a number of simulation approaches were presented. This is an outstanding example of an instance where reliance on a simulation would have led brain scientists completely astray.

Ader (1) and others have shown the value of the rat in studies on the effect of psychological factors on susceptibility to disease. Rats were used in evaluations of restraint, electric shock, and other adverse stimuli as the

cause of gastric lesions and accompanying high plasma pepsinogen levels. These studies clearly established a relationship between psychological stress and the occurrence of gastric lesions.

With rats, Tryon (99) showed that intellectual functioning was subject to genetic influences. Hall (42) produced comparable results for emotional behavior. The McGill group then manipulated environments, showing both genetic and environmental factors. The critical importance of the McGill work (69) was to show the importance of early environmental factors, a finding that gave rise to major public policies and programs.

Using rats the Yale group explored a number of hypotheses suggested by psychoanalytic thinking. Their analysis of conflict, frustration, displacement, and regression provided the first scientific base for these concepts in psychotherapy.

For the first third of the century, a fat baby was the ideal of health. A rat experiment on food deprivation was initially subject to some criticism as unnecessary cruelty, until the results revealed that the food-limited infants had much longer life spans. This was the first clue that obesity might shorten the life span and that weight patterns might be determined by early nutrition.

A matter of current interest that has not ever been formally discussed is the significant improvement in animal care and facilities seen over the past quarter century. The rat has been a standard model of aging, and in those decades the median life span of the rat has tripled. Without being explicitly mentioned, this has been one of the evidences to gerontologists that many problems of aging which were considered as normal parts of biological senescence are now being viewed as potentially remediable health problems. The rats did not change, but changes in their health status radically changed their longevity (42).

As in other fields much of the behavioral science research has not used genetically well-defined animals. Harrington (44) collected all inbred or selectively bred lines represented in the behavioral literature and available in 1962, inbred those that were not well-defined, and characterized all of the lines on the most commonly used behavioral measures. His laboratory has been a primary source for inbred animals for behavioral research in North America. The MNR, MNRA, and MR strains originally bred for emotional response are widely used for research on stress and psychopharmacology. MR and TS3 are used as a model of alcoholism. A number of strains are models for drug addictions. ACI and TS3 have been used as models for health effects of shift work in occupational health research. Despite the close historical association of the albino rat with behavioral research, pigmented rats have been more widely used in behavioral research than in other fields. Lashley and other behaviorists soon discovered deficiencies in neural development and in perceptual functions associated with albinism. Thus the majority of the lines collected and characterized by Harrington are pigmented. The implications have recently been recognized as particularly important in toxicology, where the rat is the standard animal (13a). The production of melanin and a number of neurotransmitters share common biochemical pathways. Many neurotoxicants bind to melanin so that bioassays differ markedly between pigmented and albino animals. These findings indicate that there will be an increasing use of pigmented rats for neurobehavioral applications.

Conclusions

This review has emphasized the major uses of the rat as an experimental animal for the study of disease processes and for the study of basic immunologic and genetic mechanisms. The physical characteristics of the rat make it ideal for obtaining large amounts of serum and cells and for applying various types of surgical manipulations. The definition of the structure and function of its major histocompatibility complex and the elucidation of many other aspects of its genetics have added immensely to the rat's utility in medical research. The low level of the polymorphism in the genes of the rat's major histocompatibility complex make it quite feasible to study all of the possible genetic influences on a variety of immunologic, biochemical, psychological and physiological processes and to study exhaustively the repertoire of structural variants of genetically polymorphic molecules. No other experimental animal has the combined advantages of convenient size; short gestation time; availability of a large and systematic body of immunologic, genetic, biochemical, psychological and physiological data; and a demonstrated utility in a variety of fields of biomedical research.

The section on behavioral science in this paper was prepared by Dr. Gordon M. Harrington, Dept. of Psychology, University of Northern Iowa, Cedar Falls, IA 50614.

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Biochemical Correlates of Myocardial Hypertrophy*

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ABSTRACT: Mechanisms of cardiac hypertrophy were studied in isolated perfused hearts from control animals and from rats subjected to aortic banding or induction of thyrotoxicosis. Improved efficiency of protein synthesis was observed as the result of an increase in aortic pressure from 60 to 120 mmHg in Langendorff heart preparations that were beating and developing intraventricular pressure, in hearts in which the left ventricle was drained and in hearts in which cardiac contraction was arrested with tetrodotoxin and the ventricle was drained. These effects involved faster rates of peptide chain initiation and elongation. Oxygen consumption increased as aortic pressure was raised in control-beating and beating-drained hearts, but not in arrested-drained hearts. Neither glucose availability, intracellular glucose-6-phosphate, energy availability, nor the perfusate concentration of ionized calcium could be related to the effect of aortic pressure on the efficiency of protein synthesis. Stretch of the ventricular wall, as a consequence of increased aortic pressure, appeared to be the mechanical parameter most closely related to the increase in protein synthesis.

In hearts that were hypertrophying as a result of aortic banding or induction of thyrotoxicosis, a 24% increase in the rate of protein synthesis in isolated working hearts perfused with buffer that simulated substrate and hormone concentrations of plasma was accompanied by 25% increase in ribosomal RNA content. Content of ribosomal subunits indicated that less than 12% of total RNA was in these particles in either control or hypertrophying hearts. These results revealed that increased protein synthetic machinery, as monitored by content of ribosomal RNA, rather than more efficient initiation or elongation of peptide chains accounted for the faster rate of protein synthesis in hypertrophying hearts. When rates of ribosome production were measured in vitro at various times after a single injection of thyroxine in vivo, faster ribosome synthesis was detected within 4h; no change in the rate of total protein synthesis occurred after a single injection of thyroxine. These studies demonstrated that accelerated ribosome formation was an early and quantitative important factor in cardiac hypertrophy.

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INTRODUCTION. Growth of the heart in adult animals is a process that involves muscle cell hypertrophy. For hypertrophy to occur, protein synthesis must be faster than protein degradation (for review, 27). Rates of protein synthesis are determined by the quantities of initiation, elongation and termination factors and ribosomes (capacity for synthesis) and the efficiency with which these components are used to form protein (Figure 1). The specific protein that is made reflects the relative quantities of specific mRNAs that are present. In regard to thyrotoxic cardiac hypertrophy, Dillman et al. (6) observed qualitative differences in mRNA extracted from hearts of hypothyroid and T_3-treated hypothyroid rats. The products of in vitro translation were analyzed by 2-dimensional electrophoresis and resulted in the resolution of 421 translation products. The relative predominance of eight products was increased in T_3-treated relative to hypothyroid rats, while four products were decreased. In regard to a specific mRNA, Everett et al. (9) recently reported that only myosin heavy chain β-mRNA was expressed in hearts of hypothyroid animals, but that myosin heavy chain α-mRNA represented 20%, 50% and 90% of total myosin mRNA after 12 h, 24h, and 72h, respectively, following T_3-injection. An additional factor that may result in expression of one mRNA as compared to another is competition for a factor involved in peptide-chain initiation (14). For example, in SC-1 cells, viral and host mRNAs competed for a message discriminatory component prior to their binding to the 40S ribosomal complex. A hierarchy appeared to exist in which host mRNAs had greater affinity than reovirus mRNAs for peptide-chain initiation (51).

In isolated hearts of control rats that were perfused with a buffer simulating rat plasma, only approximately 12% of total RNA was recovered in ribosomal subunits indicating that sufficient mRNA was present in these hearts to allow almost all of the ribosomal subunits to be active in protein synthesis (25-27,40). However, studies in this laboratory showed that peptide-chain initiation was regulated in heart muscle by provision of insulin, non-carbohydrate substrates (such as fatty acids, lactate, ketone bodies, and acetate), leucine, and physiologic aortic pressure development (20,25,27) but it appeared that in normal hearts, in vivo, peptide chain initiation was always rapid enough to maintain a high level of ribosomal aggregation because several of these stimulatory factors were present simultaneously in any physiologic situation. This view is in contrast to that of Zähringer and Klaubert (57) who concluded that changes in cardiac mRNA levels were the major regulatory factor in control of whole heart protein synthesis. These workers found that availability of total mRNA increased in thyroxine-induced hypertrophy by 59% while total RNA increased by 29% and suggested that mRNA had limited protein synthesis in hearts of untreated control rats. In order for whole heart protein synthesis to be regulated in this manner, control hearts should have a substantial fraction of total RNA in ribosomal subunits. As noted above, only 12% of total RNA was recovered in subunits so

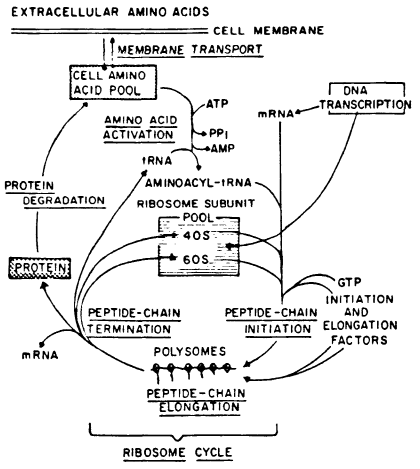

Figure 1. Pathway of protein turnover. Amino acids are supplied to the intracellular pool by either membrane transport or protein degradation. Intracellular amino acids are activated to form aminoacyl derivatives by combination with tRNA. Polymerization of activated amino acids into protein is accomplished by a series of ribosome-catalyzed reactions that make up the ribosome cycle. These reactions include initiation of peptide chains on the ribosomes and elongation and termination of chains. Peptide-chain initiation refers to binding of messenger RNA (mRNA) and initiator-tRNA (methionyl-$tRNA_f$) to the small ribosomal subunit (40S) followed by the binding of the large subunit (60S). Both steps require GTP and initiation factors. Peptide-chain elongation refers to successive addition of activated amino acids as determined by the code contained within mRNA. This process is dependent on elongation factors. When the protein is complete, the peptide chain and ribosomal subunits are released into the cytoplasm. Protein degradation refers to reactions catalyzed by proteases and results in the release of free amino acids into the intracellular pool. From Morgan et al. (27).

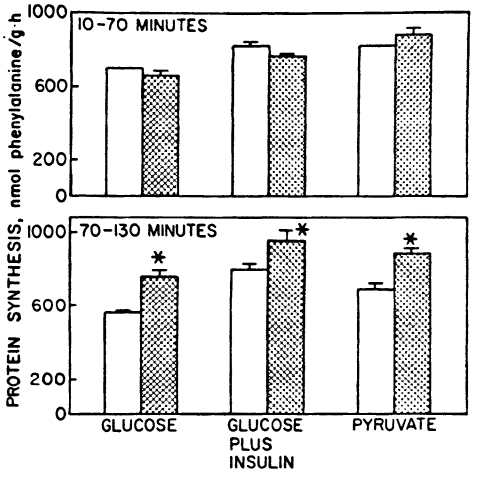

Figure 2. Effect of aortic pressure on protein synthesis in perfused rat hearts supplied glucose (15 mM), glucose plus insulin (1.7 x 10^{-8} M), and pyruvate (10 mM). Hearts were perfused initially for 10 min as Langendorff preparations with an aortic pressure of 40 mmHg with buffer that contained 0.4 mM phenylalanine, plasma levels of 19 other amino acids and the substrate indicated above. This buffer was discarded after a single pass through hearts. Perfusion was continued by recirculating 30 ml of same buffer containing 0.2% bovine serum albumin and [U-^{14}C]phenylalanine through hearts for periods indicated. When second h rates were to be measured, radioisotope was added at 70 min. Perfusion pressure was adjusted to 60 or 120 mmHg at beginning of recirculation period. Values represent the mean ± S.E. of 5 to 12 hearts. *$p < 0.05$ vs hearts perfused at 60 mmHg for same test period. Data were derived from Kira et al. (20).

that at best only a small acceleration of protein synthesis would occur if mRNA availability alone were increased. Earlier studies of RNA synthesis in hypertrophying hearts suggested that synthesis of all classes of RNA were increased, including mRNA, rRNA and tRNA (11,21,45). Thus, the bulk of evidence indicates that faster rates of protein synthesis are an important factor for rapid heart growth. Decreased rates of protein degradation do not appear to make a significant contribution (for review, 41).

Cardiac work increased the rate of protein synthesis in isolated heart preparations (18,25, 37). In these preparations, increased synthesis was associated with development of higher levels of ventricular pressure rather than increased cardiac output (18). Increased rates of protein synthesis also were observed in Langendorff preparations after elevation of aortic pressure from 60 to 120-150 mmHg (18,20,44). Cardiac arrest did not lower the rate of synthesis at either perfusion pressure (19,20, 36,44). Takala (44) and ourselves (20) concluded that the increase in aortic pressure and not workload per se was the reason for faster protein synthesis. Elevation of aortic pressure resulted in stretch of the ventricular wall (28,50), a change that accelerated the rate of protein synthesis in isolated papillary muscle (32) and in atria (42).

The purposes of the present experiments were: 1) to explore the relationship between coronary perfusion pressure and protein synthesis in Langendorff preparations and working hearts, 2) to explore potential regulators linking coronary perfusion pressure to faster rates of protein synthesis, 3) to determine the extent to which increased protein synthesis in hypertrophying hearts was the result of increased efficiency or capacity for protein synthesis, and 4) to assess the rate of ribosome production during the initial stages of cardiac hypertrophy.

EFFECT OF AORTIC PRESSURE AND HEART WORK ON PROTEIN SYNTHESIS. Elevation of aortic pressure from 60 to 120 mmHg accelerated protein synthesis during the second hour of perfusion in hearts supplied glucose, glucose plus insulin, or pyruvate (Figure 2). No effect of elevation of aortic pressure was observed during the first hour of perfusion. In other experiments, hearts were perfused at an aortic pressure of 60 mmHg in the first hour and at 120 mmHg in the second hour or, alternatively, at 120 mmHg in the first hour and at 60 mmHg in the second hour. When aortic pressure was raised from 60 to 120 mmHg at the beginning of the second hour

Table 1. Effect of perfusion pressure on levels of ribosomal subunits in hearts supplied glucose (15 mM) or glucose and insulin (1.7×10^{-8} M).

Perfusion conditions	Aortic pressure, mmHg	Ribosomal subunits µg RNA/mg homogenate RNA	
		60S	40S
Unperfused		61 ± 5	44 ± 4
Control; glucose	60	138 ± 9	78 ± 4
	120	77 ± 9	48 ± 4
Control; glucose	60	45 ± 15	28 ± 5
and insulin	120	48 ± 9	29 ± 3

Hearts were perfused as described in Figure 2. After 10 min of preliminary perfusion, buffer was recirculated for 90 min at either 60 or 120 mmHg aortic pressure. Insulin was added where indicated. Blood was washed from unperfused hearts for 1 min before homogenization. Values are mean ± S.E. of 5 to 11 observations. Data were derived from Kira et al. (20).

protein synthesis in the second hour was 640 ± 31 nmol phenylalanine/g dry heart. When aortic pressure was reduced from 120 to 60 mmHg at the beginning of the second hour, the comparable rate was 766 ± 51 nmol phenylalanine/g dry heart. These observations suggested that the increased rate of protein synthesis required at least 1h at the higher aortic pressure to develop and that the effect persisted for at least 1h after lowering aortic pressure. Similar changes in protein synthesis were observed in cardiac muscle cells that were isolated from hearts in which the rate was measured during the second hour of perfusion (20). In working hearts supplied glucose or glucose plus insulin, rates of protein synthesis were higher during both hours of perfusion than in Langendorff preparations exposed to an aortic pressure of 60 mmHg.

The effects of higher aortic pressure on peptide chain initiation and elongation were assessed by measurement of the tissue content of ribosomal subunits (Table 1). When hearts were perfused for 90 min at 60 mmHg aortic pressure and supplied glucose as substrate, content of ribosomal subunits increased, indicating development of a block in peptide-chain initiation. This block was partially overcome by elevation of aortic pressure, as indicated by an increase in the rate of protein synthesis and fall in the content of ribosomal subunits. These results indicated that higher aortic pressure would accelerate peptide-chain initiation. When glucose and insulin were provided, subunit content remained below that found in unperfused hearts indicating that insulin had accelerated peptide-chain initiation. An increase in aortic pressure accelerated protein synthesis in insulin-treated hearts, but had no effect on subunit content. These findings suggest that higher aortic pressure may also accelerate elongation and termination of peptide chains.

The next series of experiments were undertaken to identify the parameters of contractile activity that may be involved in the enhancement of protein synthesis in hearts perfused at higher aortic pressures (Figure 3). Protein synthesis was measured during the second hour in Langendorff preparations with an aortic pressure of either 60 or 120 mmHg, with or without insertion of a drain into the left ventricle, and during arrest of drained hearts with tetrodotoxin. When aortic pressure was increased from 60 to 120 mmHg, intraventricular pressure increased pro-

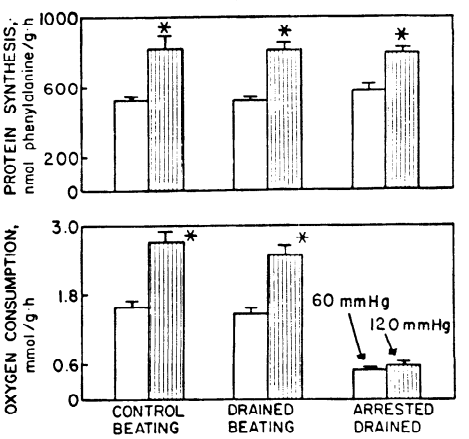

Figure 3. Effect of aortic pressure on protein synthesis and oxygen consumption in drained and arrested-drained hearts. Hearts were perfused as described in legend to Figure 2. To drain the left ventricle, a Teflon tube (18 gauge) was inserted through apex of heart. Hearts were arrested by addition of tetrodotoxin to recirculation buffer (final concentration, 9 µg/ml) and [U-^{14}C]phenylalanine was added after 70 min of recirculation to measure protein synthesis during the second hour. Oxygen consumption was measured in different hearts than those used for measurement of protein synthesis, as described earlier (Morgan et al., 1980). Values represent the mean ± S.E. of 6 to 10 hearts. Data were derived from Kira et al. (20).
*$p < 0.05$ vs hearts perfused under same conditions at an aortic pressure of 60 mmHg.

portionally, but this increase was prevented by insertion of a ventricular drain. Heart rate was not significantly different at aortic pressures of 60 and 120 mmHg or after insertion of a ventricle drain. Myocardial oxygen consumption increased as aortic pressure was raised, but was not significantly reduced by insertion of a drain. When the heart was arrested, oxygen consumption fell to approximately 0.54 nmol·g^{-1} at either aortic pressure. In Langendorff preparations perfused with an aortic pressure of 60 mmHg, prevention of intraventricular pressure development (drained-beating hearts) or cessation of both beating and intraventricular pressure development (arrested-drained hearts) had no effect on the rate of protein synthesis. When aortic pressure was raised to 120 mmHg, protein synthesis increased approximately 40% in control beating, drained-beating and arrested-drained hearts. These results indicated that there was no apparent relationship between intraventricular pressure development, myocardial oxygen consumption, or contractile activity and the faster rate of protein synthesis that was induced by elevation of aortic pressure and focussed attention on wall tension as an important factor. These effects of stretch on protein synthesis appeared to differ from effects of stretch on α-aminoisobutyric acid (AIB) uptake in tissue-cultured skeletal myotubes (47). In the myotube system, stretch-induced AIB uptake in serum-free medium was completely inhibited by tetrodotoxin, suggesting a coupling between the voltage-sensitive and stretch-induced amino acid transport. In agreement with Vandenburgh (46), stretch-induced stimulation of protein synthesis in the perfused heart did not depend upon addition of serum but involved events intrinsic to the heart.

POTENTIAL REGULATORS LINKING CORONARY PERFUSION PRESSURE TO FASTER RATES OF PROTEIN SYNTHESIS. Correlations between two groups of potential regulatory factors and the rate of protein synthesis were sought in Langendorff and working heart preparations in which the coronary beds were perfused with a range of aortic pressures. In the first group of these experiments, glucose-6-phosphate content and energy levels were measured in heart preparations supplied glucose, glucose plus insulin or pyruvate and were correlated with the rate of protein synthesis (Figure 4). Glucose-6-phosphate content was higher in hearts supplied glucose, and particularly glucose and insulin, compared with pyru-

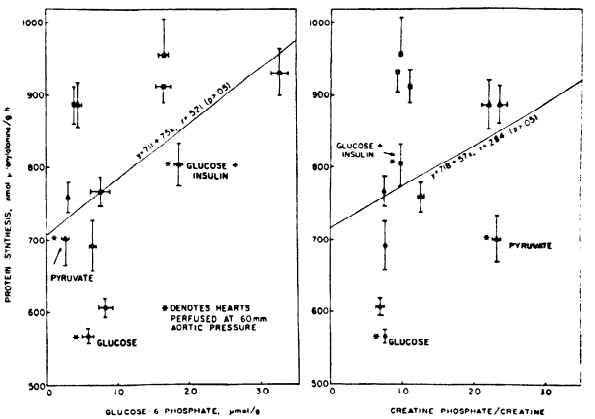

Figure 4. Correlation between levels of intracellular glucose-6-phosphate and creatine phosphate/creatine ratio and protein synthesis. Glucose-6-phosphate, creatine and creatine phosphate contents were measured in the same hearts as shown in Figure 2. Hearts supplied glucose, glucose plus insulin and pyruvate are indicated by closed circles, closed squares and triangles, respectively. The four values for each substrate indicate Langendorff preparations perfused at 60,90 and 120 mmHg and working hearts. Rates of protein synthesis during 70-130 min of perfusion were plotted as a function of average glucose-6-phosphate content or creatine phosphate/creatine at 70 and 130 min. From Kira et al. (20).

Table 2. Effect of perfusate calcium concentration on protein synthesis, oxygen consumption and energy availability.

Parameter	Ionized perfusate calcium (mM) 0.5	2.9	5.0
Protein synthesis (nmol phenylalanine/g·h)	757±33 (4)	664±26 (10)	700±34 (10)
Oxygen consumption (mmol/g·h)	1.47±0.08 (7)	2.24±0.11 (8)*	2.98±0.41 (5)*
Creatine phosphate/ creatine	1.97±0.21 (6)	0.877±0.087 (5)*	0.761±0.058 (5)*

Hearts were perfused as Langendorff preparations at an aortic pressure of 90 mmHg with buffer that contained 15 mM glucose, 0.4 mM phenylalanine, normal plasma levels of amino acids, 0.1 mM EDTA and the ionized calcium concentration that is indicated. After 70 min of perfusion, [U-^{14}C]phenylalanine was added, and perfusion was continued for 60 min for measurement of rates of protein synthesis. When oxygen consumption was measured, the pulmonary artery was cannulated, and samples of arterial and venous perfusate were collected for measurement of oxygen tension. Creatine phosphate and creatine were measured in perchloric acid extracts of heart. Values are the means ± S.E. of the number of observations shown in parenthesis. Data were derived from Gordon et al. (15).
*$p < 0.05$ vs 0.05 mM Ca.

vate. Despite the lower glucose-6-phosphate content, rates of protein synthesis were higher in hearts supplied pyruvate rather than glucose at each aortic pressure. The increases in synthesis induced by either increased aortic pressure or heart work in preparations supplied glucose or pyruvate were not associated with an elevation of the average glucose-6-phosphate content. In the presence of insulin, only the acceleration of synthesis in working hearts was accompanied by higher glucose-6-phosphate. Overall, there was not a significant relationship between glucose-6-phosphate and the rate of synthesis (Figure 4). Similarly, there were no consistent changes in ATP, ADP, AMP, creatine, creatine phosphate, ATP/ADP ratio, adenylate energy charge, or creatine phosphate/creatine ratio, as aortic pressure was raised from 60 to 90 or 120 mmHg in Langendorff preparations or cardiac work was induced (20; Figure 4). In general, energy levels were higher in hearts supplied glucose and insulin or pyruvate than in those supplied glucose (Figure 4). Overall, there was not a significant correlation between creatine phosphate/creatine and protein synthesis in these experiments. These results suggest that changes in glucose-6-phosphate or energy levels did not mediate the enhancement of protein synthesis caused by an increase in aortic perfusion pressure or cardiac work.

The next series of experiments was undertaken to determine whether variations in perfusate ionized calcium within the range that maintained cellular integrity in beating hearts could modify rates of protein synthesis, oxygen consumption and energy availability (15). When the ionized calcium concentration was reduced below 0.5 mM, the heart lost protein and nucleotides into the perfusate and became white and markedly swollen. Solubility of calcium in bicarbonate buffer restricted the use of calcium concentrations higher than 5 mM. An increase in extracellular ionized calcium from 0.5 to 5.0 mM had no effect on protein synthesis during the second hour of perfusion (Table 2). An aortic pressure of 90 mmHg was chosen because it approximated mean aortic pressure, in vivo, and glucose was selected as substrate because this substrate supported rates of protein synthesis that were not maximal. Although rates of protein synthesis were unaffected by an increase in extracellular calcium from 0.5 to 5.0 mM, oxygen consumption doubled, and the creatine phosphate/ creatine ratio decreased by approximately 50%. These experiments failed to demonstrate an effect of the availability of extracellular calcium on protein synthesis even though heart rate (data not shown) and oxidative metabolism were markedly increased as extracellular calcium was raised. A reservation in the interpretation of these experiments is that an effect of high extracellular calcium on protein synthesis may have been obscured by the decrease in energy availability.

The effect of extracellular calcium availability was examined in a second group of experiments to determine whether the response of protein synthesis to increased aortic pressure would be modified (Table 3). The arrested-drained heart was selected for these studies to minimize the effect of calcium concentration on contractile activity and energy metabolism. An increase in aortic pressure from 60 to 120 mmHg accelerated the rate of protein synthesis to the same extent at each perfusate calcium concentration, but had no effect on creatine phosphate/creatine ratio at either 0.5, 2.9 or 5.0 mM calcium.

The biochemical parameters that were measured in an effort to determine whether they might play a role in the effect of aortic pressure

Table 3. Effect of aortic pressure on protein synthesis and energy availability in arrested-drained hearts supplied glucose and a range of calcium concentrations.

Ionized perfusate calcium mM	Aortic pressure, mmHg	Protein synthesis nmol phenylalanine/g·h	Creatine phosphate/ creatine
0.5	60	608 ± 35	2.24 ± 0.16
	120	710 ± 28[a]	2.73 ± 0.16
2.9	60	608 ± 59	1.01 ± 0.05
	120	771 ± 36*	1.03 ± 0.09
5.0	60	517 ± 45	1.16 ± 0.13
	120	726 ± 39*	1.41 ± 0.16

Hearts were perfused as described in Table 1. Rates of protein synthesis were measured during 70-130 min of perfusion and creatine phosphate/creatine was measured at 130 min. Cardiac contractions were arrested by addition of tetrodotoxin (9 μg/ml), and an 18-gauge Teflon catheter was inserted through the apex to prevent accumulation of fluid and pressure development in the ventricle. Values are the means ± S.E. of 6 hearts. Data are from Gordon et al. (15).

*$p < 0.05$ vs 60 mmHg.

on the efficiency of protein synthesis were glucose-6-phosphate content, energy availability and extracellular calcium concentration. The inhibition of peptide-chain initiation in hearts supplied glucose may have resulted from decreased formation of the eIF-2·met-tRNA$_f^{Met}$·GTP ternary complex due to reduction in GTP/GDP ratio (52), a reflection of the ratio of creatine phosphate to creatine. However, in control-beating hearts (Figure 4) or arrested-drained hearts (Table 3), the increase in protein synthesis induced by higher aortic pressure was not accompanied by an increase in creatine phosphate/creatine ratio. Similarly, glucose-6-phosphate was found to accelerate peptide chain initiation in reticulocyte lysates (8), but no relationship was found between glucose-6-phosphate content in perfused rat hearts and the effect of aortic pressure on protein synthesis. The effect of calcium availability on protein synthesis in heart muscle has been studied in only a limited manner. In guinea pig hearts, Schreiber et al., (38) reported that an increase in perfusate calcium concentration from 0.6 to 4.8 mM had no effect on the incorporation of lysine into protein of guinea pig hearts that were perfused in vitro. The present experiments confirmed and extended these findings by showing that an increase in extracellular calcium concentration from 0.5 to 5.0 mM increased heart rate and oxygen consumption in beating hearts and decreased energy availability, but had no effect on the rate of protein synthesis (Table 2). In arrested-drained hearts supplied glucose, rates of protein synthesis at 120 mmHg aortic pressure averaged 28% higher than at 60 mmHg over the range of calcium concentrations from 0.5 to 5.0 mM. Overall, these experiments provided no support for the possibility that calcium availability was an important controlling factor for myocardial protein synthesis.

INCREASED EFFICIENCY AND/OR INCREASED CAPACITY AS THE FACTORS ACCOUNTING FOR FASTER PROTEIN SYNTHESIS IN HYPERTROPHYING HEARTS. The results that have been presented thus far indicate that exposure of isolated hearts to higher aortic pressures increased the efficiency of protein synthesis after a lag of about 1h. However, the question remains as to whether hypertrophying hearts synthesize protein more rapidly than control hearts because of improved efficiency (nmol phenylalanine incorporated/mg RNA·h), higher capacity (mg RNA/g heart), or both. To explore this question, hearts were perfused as working preparations with buffer that simulated normal plasma levels of substrates and hormones (Table 4). Under these conditions, the faster rate of protein synthesis in hypertrophying hearts appeared to be a function of the quantity of protein synthetic machinery, as monitored by the content of ribosomal RNA. Greater capacity rather than greater efficiency accounted for the approximately 24% increase in protein synthesis in hearts from animals with aortic bands or thyrotoxicosis. As noted in the introduction to this paper, only approximately 12% of total RNA was recovered in ribosomal subunits from hearts of either saline-injected (perfused or unperfused), thyroxine-injected or aortic-banded rats that were perfused under these simulated in vivo conditions (40). These findings indicated that there were no changes in the balance between rates of peptide-chain initiation and elongation due to hypertrophy when hearts were perfused under simulated in vivo conditions and that sufficient mRNA was present in these hearts to allow almost all of the ribosomal subunits to be

Table 4. Rates of protein synthesis in control and hypertrophied hearts.

Condition of animals	Heart weight, mg dry wt.	Protein synthesis, nmol phenylalanine/g·h	Ribosomal RNA, mg/g	Efficiency, nmol phenylalanine/mg RNA·h
Untreated	154±4(6)	735±20	5.80±0.10(5)	127
T_4-injected, 4 days	167±4(8)*	915±31*	7.20±0.15(6)*	127
Sham-operated	146±7(5)	698±54	6.35±0.50(4)	110
Aortic-banded, 3 days post-operative	182±7(6)$^+$	864±17$^+$	8.00±0.40(3)$^+$	108

Hypertrophy was induced by partial occlusion of the aorta or daily intraperitoneal or subcutaneous injections of thyroxine (1 μ/g rat) (40). Hearts were perfused first as Langendorf preparations (10 min) and then as working preparations as described by Morgan et al. (25), with Krebs-Henseleit bicarbonate buffer that contained 0.1% bovine serum albumin, 10 mM, glucose, 2 mM lactate, 2.8×10^{-9} M insulin (400 μg/ml), normal plasma levels of 19 amino acids and 0.4 mM [U-^{14}C]phenylalanine (0.1 μCi/ml). Ribosomal RNA was isolated, processed, and characterized as described elsewhere (40). Values represent the mean ± S.E. for the number of hearts indicated in parenthesis. Data are from Siehl et al. (40).

*$p < 0.05$ vs untreated

$^+p < 0.05$ vs sham-operated.

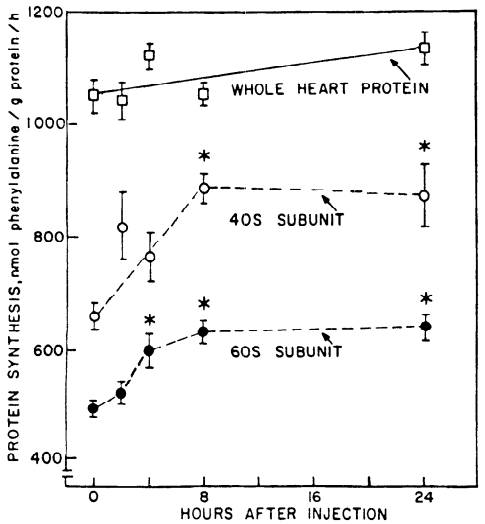

Figure 5. Rates of synthesis of whole heart protein and ribosomal protein following a single injection of thyroxine. Rats were injected subcutaneously with thyroxine (1 mg/kg body weight). At the times indicated, hearts were excised and perfused for 2 h as Langendorff preparations with an aortic pressure of 60 mmHg with buffer that contained 2.8 x 10^{-9} insulin, 50 μM bathocuproine disulfonate, 20 mM glucose, 0.1% bovine serum albumin, and normal plasma levels of amino acids, except 0.4 mM L-(ring-2,6-^{3}H]phenylalanine (25 μCi/ ml) (40). At the end of the labelling period, hearts were perfused for an additional 4 min in the presence of 70 μg puromycin/ml to improve yield of total ribosomal subunits during homogenization (26). Ribosomal subunits were extracted and purified as described by Siehl et al. (40). Following a lag of 10-12 min, rates of ribosomal protein synthesis were linear over the 2 h of perfusion. Values represent the mean ± S.E. of 7 to 9 hearts at each time point. From Siehl et al. (40).
*$p < 0.05$ vs zero hours, as determined by analysis of variance, followed by Student-Neuman Keuls test of significance.

active in protein synthesis (25,27,40). Accelerated synthesis, decreased degradation or a combination of both events are assumed to account for higher tissue levels of rRNA, ribosomes, mRNA and presumably enzymes involved in peptide-bond formation.

RATES OF RIBOSOME PRODUCTION DURING THE INITIAL STAGES OF CARDIAC HYERTROPHY. Tissue levels of ribosomes in the hypertrophying rat heart depend upon the balance between rates of pre-ribosomal RNA synthesis, processing and rRNA degradation and between rates of synthesis and degradation of ribosomal proteins. Shifts in these balances are suggested to account for the greater concentration of ribosomes that are found in hypertrophying hearts (for review, 40,41). Rigorous determinations of rates of ribosomal protein and ribosomal RNA synthesis have only recently been undertaken in heart, and the control mechanisms are largely unexplored. These rates depend upon knowledge of the specific activities of the immediate precursors, amino acids bound to tRNA in the case of ribosomal proteins and specific nucleotides within pre-ribosomal RNA in the case of ribosomal RNA.

The final experiments were undertaken to determine the effect of thyroxine on rates of synthesis and incorporation of ribosomal proteins into newly-made cytoplasmic ribosomes. The increase in tissue content of ribosomes in hearts from T_4-injected rats was due, at least in part, to formation of new ribosomes (Figure 5). Ribosome production accelerated approximately 30% as measured by incorporation of [^{14}C]phenylalanine into proteins of cytoplasmic ribosomes, within 4h after a single injection of thyroxine (40). No change in the synthesis of whole heart protein was detectable in the first 24h after hormone injection. When a second injection of thyroxine was given 24 h later, ribosome production had doubled (data not shown). This situation is different from that reported for compensatory renal hypertrophy in the mouse where ribosomal protein synthesis increased in proportion to synthesis of total renal protein, and increased ribosome content was suggested to be due to conservation of ribosomes that otherwise would have been degraded (23). In livers of five days protein depleted mice, refeeding of these animals restored ribosome content within one day by accelerating ribosome formation and almost totally blocking ribosome degradation (3). Restoration of ribosome content in regenerating rat liver involved not only faster ribosomal RNA synthesis, but almost complete inhibition of cytoplasmic ribosomal degradation (29). In Tetrahymena, refeeding of starved cells resulted in an increase in the percentage of proteins synthesized that were ribosomal from 3% to 40% within 2h (16). This increase appeared to be due to formation of ribosomal protein mRNA, as assessed by translationally active mRNAs for ribosomal protein in a wheat germ extract (7).

Ribosome production involves the coordination of the transcription of ribosomal RNA and ribosomal protein mRNA, nuclear processing of these transcripts, and cytoplasmic translation of the ribosomal protein mRNAs (55). Methods must be available for measuring the rates of synthesis of ribosomal RNA and ribosomal proteins independently in heart muscle, so that each can be studied separately. Ribosomal DNA is present in hundreds of copies, tandemly arranged head to tail along the dense nucleolar chromatin (for review, 22). The genes are transcribed by RNA polymerase I into 45S pre-ribosomal RNA. The pre-ribosomal RNA undergoes processing, mainly in the nucleolus, involving several cleavages, methylation, and binding of the ribosomal proteins (for review, 53). In some systems, not all of the pre-ribosomal RNA was processed into mature ribosomal RNA, but instead was degraded by intracellular nucleases. This so-called "wastage" was apparent as a site of regulation of ribosomal RNA content in cultured human lymphocytes (4), renal hypertrophy (17), regenerating liver (35), and valine deprivation in fibroblasts and liver cells (34,49). Wastage was not observed, however, in Tetrahymena in which both growing and starved cells converted all of pre-ribosomal RNA to mature RNA (43). Similarly, wastage did not occur in normal or regenerating liver, but rather a 2.7-fold increase in transcription completely accounted for the faster ribosome production (5). Future studies should define whether decreased rRNA wastage is an important factor in accumulation of more ribosomes in hypertrophying hearts.

It is anticipated that the regulation of rRNA production in the heart will be found to be related to that of ribosomal protein production, but virtually nothing is known of the factors that regulate production of ribosomal components in the heart. The best defined model system is E. coli, where it has been found that ribosomal proteins are encoded in clusters on several mRNAs (30). Each message has a ribosome entry site that can be blocked by one particular free ribosomal protein, coded by the same message. When ribosomal RNA synthesis slows, the repressor ribosomal protein begins to accumulate and bind to the ribosome entry site of its own message, blocking the translation of itself and other ribosomal proteins coded by that message. The synthesis of ribosomal RNA is apparently controlled indirectly by the activity of peptide chain initiation. Slower initiation, induced by a shift to poorer growth conditions, results in accumulation of free ribosomal subunits that appear to be capable of inhibiting transcription of pre-ribosomal RNA. Thus, E. coli have two negative feedback loops, one for ribosomal RNA synthesis, controlled by free ribosomal subunits, and one for ribosomal protein, controlled by free ribosomal proteins through translational repression. It is unknown whether a similar mechanism operates for coordination of production of ribosomal proteins in higher eukaryotes. Another consideration is that ribosomal protein synthesis takes place in the cytoplasm of eukaryotic cells and ribosomal RNA synthesis takes place in the nucleus; any competition between ribosomal protein mRNA and ribosomal RNA for "repressor" ribosomal proteins might be hindered by the presence of the nuclear membrane. In HeLa cells, synthesis of ribosomal proteins continued at a normal rate for 30 h after ribosomal RNA synthesis was virtually blocked by a low dose of actinomycin D (54). The converse, in which pre-ribosomal RNA formation proceeded in the virtual absence of ribosomal protein synthesis has also been observed in temperature-sensitive mutants of yeast which are unable to synthesize ribosomal protein mRNA at a non-permissive temperature (39). As in E. coli, the synthesis of most ribosomal proteins is probably balanced and coordinately regulated (for review, 55). Therefore, one may ask about the mechanism responsible for coordination in eukaryotic cells. By the use of recombinant DNA techniques, several genes for ribosomal proteins were cloned from yeast (1,12, 56), Drosophila (10,48), Xenopus (2), and mouse (24), and it has become possible to measure the amount, as well as the synthesis and decay rates, of ribosomal protein mRNA. As a result, regulation of the translation of ribosomal protein mRNA has been found in developing embryos of Xenopus (33), in cultured mouse cells during the transition from resting to serum-stimulated states (13), and in yeast cells (31). Future work should allow for determination of the template activity and mRNA content for ribosomal proteins, rigorous estimates of rates of ribosomal protein synthesis and incorporation of ribosomal protein into cytoplasmic ribosomes, and measurements of rates of synthesis of pre-ribosomal RNA and processing of this molecule to mature ribosomal RNA in heart muscle. As a result, the steps of new ribosome formation that are accelerated early in growth of the heart should be identified.

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Joint Meeting of The Physiological Society and The American Physiological Society Physiological Laboratory University of Cambridge, England September 12–14, 1985

The following information is provided to assist APS members planning to attend the meeting to be held at the Physiological Laboratory, University of Cambridge, England, September 12–14, 1985.

1. Format of meeting

a) One day of the meeting will be devoted to a symposium on "Transduction at the receptor level in the visual and auditory systems," in honor of Sir Alan Hodgkin, organized by Professor Richard Keynes. The proposed list of participants includes J. A. Ashmore (Bristol), D. Atwell (London), D. A. Baylor (Stanford), L. Cervetto (Pisa), A. C. Crawford (Cambridge), R. Fettiplace (Cambridge), A. Flock (Stockholm), A. L. Hodgkin (Cambridge), A. J. Hudspeth (San Francisco), H. G. Khorana (MIT), M. Kuhn (Julich), T. Lamb (Cambridge), P. McNaughton (Cambridge), and I. J. Russel (Sussex).

b) The remaining two days will be devoted to contributed papers in oral and poster sessions, with the sessions shared equally between the British and US Societies.

c) In conformity with the practice of our hosts, oral presentations will be divided into three approximately equal groups: neurophysiology, biophysics (including organ system membrane transport studies), and other topics (referred to by the British as "the rest"). The poster sessions will be of a more general nature, with no restrictions on the mix of categories.

d) Space and time constraints will limit the number of contributed papers that can be accepted in any category. Accordingly, abstracts will be accepted in the order of receipt at the APS headquarters, until the allocation of any particular category has been filled. Papers submitted for presentation in an oral session will be transferred to the poster category if it is indicated that this is an acceptable alternative and provided that the allocation for posters has not been filled at the time the abstract is received at APS headquarters. A similar procedure will be used to transfer abstracts submitted for poster presentations to an oral presentation category if the poster category is filled and the oral presentation category is incomplete at the time the abstract is received. Abstracts not clearly marked as accepting alternative forms of presentation if necessary will not be accepted if the category of submission is filled at the time of receipt. To facilitate abstract selection in time for publication in the program, a **deadline date of June 1, 1985** has been established for receipt of abstract at APS headquarters.

2. Submission of abstracts and presentation of papers

a) An abstract should be prepared so that, after being set in type, it will occupy not more than one full page in the *Journal of Physiology.* To achieve this, the complete abstract, including title, authors' names and addresses, tables, references and legends should be typed, in 12-point type and one and one-half line spacing, in an area 18 cm wide and 27 cm long. A blank line must be left between the title and the start of the text, and there must be a gap of one line space both at the top and bottom of figures and tables. The text may include illustrations at approximately the same size as they would appear in the *Journal of Physiology.* If an illustration does not fill the full width of the page, the space on either side must be kept clear of text. A copy of the illustration enlarged to twice its final size should be submitted with the abstract. APS members intending to submit an abstract are advised to examine a recent issue of the *Journal of Physiology* for the format used for printed abstracts. A form for preparing abstracts is available from APS headquarters.

b) When the list of authors on an abstract includes more than one name, the authors names will be listed in alphabetical order.

c) Only one abstract per member will be accepted for the program.

d) The format for presentation of oral papers at meetings of The Physiological Society is generally similar to

King's College Chapel, University of Cambridge

that used at APS meetings, with 10 minutes allowed for the presentation and 5 minutes for the discussion. However, the British society utilizes two practices that may be unfamiliar to APS members. First, The Physiological Society favors extemporaneous presentations, and the society rules include a statement that "No communication shall be read." Second, at the conclusion of discussion following a presentation, the chairman will ask if the author wishes the abstract to be published in the *Journal of Physiology.* Provided the author responds affirmatively, the chairman will then solicit approval of the proposal from the audience.

3. Travel and accommodation

a) APS is not able to make travel arrangements for members planning to attend the meeting, and members are encouraged to consult travel agents individually. Cambridge is readily accessible by road or British Rail from London and other regional centers.

b) Accommodation can be arranged at King's College or Pembroke College at approximately $20 per night per person for a private room with bath. APS members wishing to make reservations for these accommodations should return the attached reply card to APS headquarters.

c) Lunches, teas, a reception, and a banquet, at modest cost, will also be held in conjunction with the meeting, and APS members wishing to attend these functions should so indicate on the enclosed reply card.

d) Members who do not wish to take advantage of the accommodations available at the colleges and, in particular, handicapped individuals or members accompanied by children under 14 years of age should make independent arrangements through a travel agent for accommodation at a hotel, of which there are several in Cambridge.

4. No registration fee

Attendees will not be charged a registration fee.

APS Sections

Establishment of a Physiology Teaching Section Within APS is Proposed

Within the past several years, the "Learning Resource" area at the Spring FASEB meetings has served as a gathering place for physiologists who share common problems in teaching but whose research areas are quite diverse. With recent technological advances, more curriculum review at many institutions, and an ever-increasing knowledge base that must be mastered by students in an ever-decreasing time frame, it is clear that more attention must be paid to improving physiology teaching. The excitement generated by discussion in the Learning Resource area of the meetings suggests that the time has come to provide a broader forum of exchanging ideas relevant to physiology teaching. A group of APS members feel that a section within the Society is needed to guide movement in this direction.

The proposed section would compliment rather than conflict with the charge and activities of the APS Education Committee. The majority of Education Committee duties are aimed at continuing education for Society members (e.g., the Fall meeting refresher course), recruiting students into physiology (e.g., career opportunities literature), and materials development (e.g., audiovisual aids).

The APS Operational Guide (p. 60) states that "upon acceptance by Council of a Statement of Organization and Procedures in accordance with the Bylaws (Article X, Section 1), any group of members of the Society may form a Section that encompasses an area of physiology. The required membership for a Section is 100." With the establishment last year of the History of Physiology Section, the phrasing "encompass an area of physiology" can be interpreted to mean an area of interest common to APS members.

A meeting for the purpose of developing a Statement of Organization and Procedures has been scheduled in Anaheim during the FASEB meeting. The specific time and place will appear in the FASEB program.

All APS members interested in a section focused on improving physiology teaching are encouraged to write to Harold Modell at the address below so that a tentative list of section members may be developed. Section membership does not increase annual APS dues and does not preclude membership in other APS sections.

Harold Modell
Virginia Mason Research Center
1000 Seneca Street
Seattle, WA 98101

Establishment of a New Muscle Group

A new Muscle Group has been formed under the leadership of Dr. Marion Siegman and is to be known as the MYOBIO Group. Because the number of papers presented at APS meetings dealing with muscle and the contractile process in general has dwindled during recent years and because the topics presented were so diffuse as to complicate planning of sessions, some positive action had to be taken.

With the approval of over 200 polled APS members, MYOBIO was formed. Based on their suggestions, a Steering Committee was formed whose members include Robert Eisenberg, Richard Moss, Jack Rall (skeletal muscle), Fred Fay, Alan Jones, Marion Siegman (smooth muscle), and Alex Fabiato, Mel Lieberman, John Solaro (cardiac muscle). Among the immediate goals are *1*) the planning of symposia and workshops dealing with various aspects of muscle contraction along themes that will attract investigators from various disciplines (i.e., biophysics, chemistry, pharmacology) and *2*) a breakaway from the very orthodox organ system orientation. It is hoped that these measures will encourage cross-talk among muscle "types" and serve as an impetus for new avenues of investigation. Any interested members of APS may join MYOBIO; please contact Dr. Siegman so that your name may be added to the mailing list. The first social activity will take place at a cocktail party with the Cell and General Physiology Section on Wednesday, April 24, 1985, at 6:30 PM at the Disneyland Hotel, Anaheim.

Marion Siegman
Muscle Physiology Group

FASEB Spring Meeting
Anaheim, CA
April 21–26, 1985

APS Scientific Sessions

2,109 volunteered papers have been programmed by the APS Program Advisory and Executive Committees into 71 slide, 62 poster and 3 poster-discussion sessions. Comparable to FASEB 1984, 61.91% of the contributed papers were designated for poster-type accommodation.

The APS Theme Symposium on "Ganglionic Control of Autonomic Effector Systems" consists of 9 sessions, spanning the FASEB 1985 program week.

Histoanatomy and phenotypic development in autonomic ganglia
Neuropeptides: localization and function in autonomic ganglia
Neurochemistry of autonomic ganglia
Synaptic interactions in sympathetic ganglia
Synaptic interactions in parasympathetic and enteric ganglia
Autonomic neuroeffector transmission in smooth muscle effectors
Ganglionic control of secretory and absorptive epithelia
Neuropathology of autonomic ganglia
Central autonomic command centers

25 sessions of APS section-sponsored symposia are scheduled including

Clearance and recycling of the lung surfactant
Atrial natriuretic factor—Sessions I and II
Neuroendocrine mechanisms of plasma volume regulation
Neuroscience and human disease
- Session I. Myasthenia gravis and other diseases of nerve and muscle
- Session II. Genetic diseases of the nervous system
- Session III. Alzheimer's disease

Update in cardiovascular neurobiology
- Session I. Functional neuroanatomy
- Session II. Neurophysiology and neurotransmitters
- Session III. Central cardiovascular actions of humoral factors
- Session IV. Neurogenic factors in normal and disease states

Neural control of pancreatic function: physiologic significance
Single-channel measurements in epithelia
Physiological roles of the intrarenal renin-angiotensin system
Urea transport: renal and red blood cells
Role of the endothelial cell in the regulation of microvascular permeability to molecules
Pulmonary macrophages: role in host defense and in lung injury and repair
- Session I. Receptors and cell-cell interaction
- Session II. Sensory products

Biology of sweat glands
Membrane ATPase function in vascular muscles in hypertension
Interaction of peptides with the brush border membrane
Anaerobiosis, lactate, and gas exchange during exercise—Sessions I and II
Muramyl peptides as modulators of sleep, temperature, and immune responses
Neuromodulators and respiratory control

APS is cosponsoring three additional symposia: with the Society for Mathematical Biology, Membrane channel kinetics; and with the Biomedical Engineering Society, New approaches in imaging—study of physiologic function, and Blood gas measurements—new and noninvasive methods. As an APS guest society, the BMES is sponsoring symposia on

Microelectronics in physiology
Optical techniques for biomedical problems
Engineering and quantitative methods in microcirculation

A special feature is the APS-sponsored intersociety William Beaumont Bicentennial Symposium, "Roots and Shoots of American Experimental Biology."

APS Plenary Session
Physiology in Perspective
Walter B. Cannon Memorial Lecture
Wednesday, April 24, 1985
Convention Center, Anaheim Room

9:00 A.M. The Language of Polypeptides and the Wisdom of the Body
Roger Guillemin, Chairman
Neuroendocrinology Laboratories
Salk Institute
San Diego, CA

10:00 A.M. APS Business Meeting
John B. West, President
American Physiological Society

The APS Committee for Liaison with Industry has sponsored a symposium on "The use of animals and adjuncts in biomedical research."

There will be two scientific sessions devoted to "Computer-based education in biomedical science."

Following the Respiration Section Dinner, an evening program has been planned in tribute to several of the founders of techniques for measuring blood gas volume and acid-base concentration. The contributions by Astrup, Bean, Stow, and Clark are among those to be presented in a minisymposium on "History of blood gas and acid-base measurement."

The Women-in-Physiology sponsored lecture is "Sex hormones and behavior" to be delivered by Dr. Cathy Olson of NSF.

Continuing the History of Physiology Lecture Series, Dr. Rachmiel Levine (City of Hope National Medical Center, Duarte, CA) will discuss the "Development of our knowledge of the pancreas as an endocrine gland" as introduction to the scientific session on insulin programmed by the Endocrinology and Metabolism Section.

Again this year the APS and ASPET are cosponsoring an after-hours NIH workshop on "Program emphases and mechanisms for support of training and research on digestive diseases by the NIADDK, NIH."

APS Special Functions
Disneyland Hotel

Monday, April 22
- APS Editorial Boards Reception and Dinner

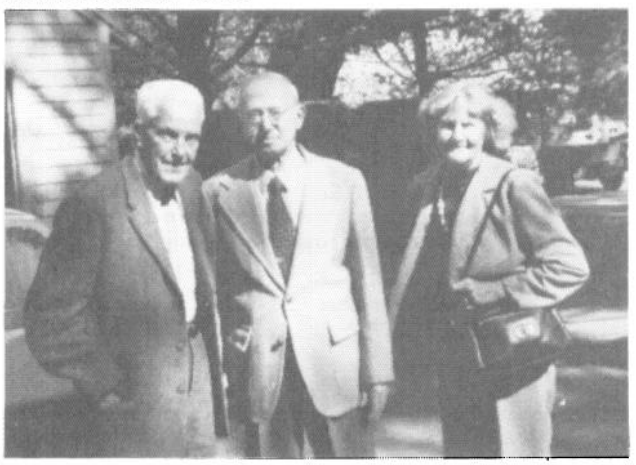
Tuesday, April 23
- Endocrinology and Metabolism Section Dinner
- Epithelial Transport Section Meeting
- Gastrointestinal Section Meeting and Social
- Respiratory Section Dinner
- Temperature Regulation Dinner
- Water and Electrolyte Homeostasis Section Meeting

Wednesday, April 24
- Cardiovascular Section Dinner (Anaheim Hilton Hotel)
- Cell and General Physiology Section Dinner
- Circulation Research Dinner
- History of Physiology Luncheon
- Neural Control Social
- Renal Section Dinner
- Regulation of Respiration Dinner
- Women in Physiology Lecture and Social

Arlie V. Bock (1888–1984)

Readers of *The Physiologist* [24(1): 11-13, 1981], may recall that at age 89 Arlie Bock gave up mowing his lawn and moved to Holden, Massachusetts, to live with his son's family (John and Shirley Bock). I had corresponded with him frequently over the years. In 1981 I wrote Arlie that Chloris and I would visit Boston in October and hoped to see him. He was happy at the prospect and as the appointed day approached, he arranged with our one-time associate Lewis Hurxthal to come from his home on Cape Cod for the reunion. We rented a car and Chloris found her way to Holden, a few miles north of Worcester.

She located Wachusetts St. but not No. 56. So we telephoned and told John, Arlie's son, where we were. He arrived shortly in his jeep and led us to his grand home in the woods. I found our colleague of 1926. Lewis Hurxthal had arrived with his daughter as driver. One of the pictures (see below) that he took shows Chloris (*right*) with Arlie at 93 years of age (*center*), and me at age 90 (*left*). During the visit indoors Arlie and Lewis showed me with great pride the illustrated volume describing their Harvard Unit No. 5 of an Army Base Hospital in France, World War I. Both Arlie and Lewis had been members of the staff.



Shortly, Shirley loaded us into vehicles and led us over winding roads through the woods to a country inn where we had an excellent lunch and reminiscent conversation.

Arlie and I continued our correspondence. His last letter dated March 29, 1984 is worth recording:

> "Dear Bruce and Chloris: It started snowing here about midnight and is still at it, with wind blowing in all directions. We haven't had a storm like this for a long time. We must have at least 6 inches but I am judging this from the amount I have to clear from the top of my bird feeder. If you think you ever had a hard time, think of my birds. I try to keep a small feeder clear to keep at least a few alive.
>
> "We are really having an experience not common to this part of the country, but for one who can sit indoors and watch the uncontrolled flight of masses of snow flakes, life is renewed. Believe it or not, with it all I am having a draught of beer.
>
> "Did I write you about my new experience in having the pleasure of reading again Steve Horvath's very interesting story about the Fatigue Lab? In this book there is a fascinating picture of D. B. Dill, which I am pleased to see. Also I find much of interest about our old friend L. J. [Henderson]. As a director of this great lab, you must have had an interesting experience. It all now seems so long ago. You are fortunate to keep pace as well as you do.
>
> "Everyone here, O.K. John gets to work with his jeep and snowplow. I couldn't face a walk in this weather.
>
> "I hope both of you are faring well. With love and best wishes, Arlie B."

On August 10, I had a letter from Arlie's son John about his dad's health. Arlie had not written me in the fall of 1983 that he had a bout of congestive heart failure from which he recovered after a week in the hospital. John added that in May he had "another episode and since then has not been too well, although he was still enjoying his rides, short walks, feeding the birds, dinners out with friends, and reading."

But in mid-July, Arlie had a fall and fractured his upper right arm. "This fractured arm seemed to be the crowning blow."

After a few days in the hospital he was transferred to the Holden Nursing Home on July 27. John's premonition was correct. He called on August 11 to say that Arlie had died that morning.

I am desolated by the loss of my best friend for the past 59 years. I feel some satisfaction that my appraisal of his role as a physiologist was written in time for him to read it. I should have added in it that I was confident that Arlie's pioneering research in the physiology of exercise generated in L. J. Henderson the concept of the Harvard Fatigue Laboratory.

Arlie was proud of me and of that laboratory. In his last letter quoted above he reported pleasure in reading the account of that laboratory written by my son-in-law and daughter, Steve and Betty Horvath.

D. Bruce Dill

George Alexander Feigen (1916–1983)

George Alexander Feigen, Ph.D., Professor of Physiology at Stanford University, died suddenly on May 22, 1983.

George Feigen was born in Rostov-on-Don in 1916. The Revolution forced the Feigen family to leave Russia, and life thereafter became an odyssey which took George to Germany, to Shanghai, to Mexico and finally in 1930 to this country, and after a period in Chicago, to California. As a consequence of these experiences, he was able to apply his natural proficiency for languages and became fluent in several, especially Spanish. He maintained a lifelong love of travel, which he shared with his wife.

He graduated in physiology from Berkeley in 1938 and then moved to Pasadena where he held a series of predoctoral appointments at the California Institute of Technology. Some of those with whom he came into contact in Pasadena were to influence him through the whole of his professional life, particularly Dan Campbell and Linus Pauling. He received his Doctorate from

Cal Tech in 1947 for studies of plasma substitutes, and then after a year as a teaching fellow there and another year at the University of Southern California as a Research Associate in Pharmacology, he joined the Department of Physiology at Stanford as an Instructor. Apart from periods away on sabbatical leave, he spent his professional life at Stanford.

His investigative work displayed considerable diversity. Certainly his most important contributions were to knowledge of the acute immune response, particularly to factors involved in anaphylaxis and the mechanisms by which heart muscle and other tissues are involved in these reactions.

"Cardiac anaphylaxis," a term introduced by him in the 1960's, refers to the reaction that ensues when the guinea pig heart is challenged in vitro with the sensitizing antigen. Feigen demonstrated that histamine is a major mediator of anaphylactic cardiac dysfunction. His poineering work constitutes the basis of our current hypothesis that hypersensitivity mediators, including histamine, cause cardiac dysfunctions in humans and may play a role in the pathogenesis of sudden cardiac death, heart attacks, and cardiac failure.

In recent years, work in his laboratory had been directed increasingly to examination of the influence of steroid hormones and vitamin C on humoral and cellular immunity and the pathways involved in these interactions.

George Feigen was an impressive man. As a teacher, he commanded respect and yet was informal and without pretension. He demanded the highest standards of himself and his students in the laboratory. His curiosity and enthusiasm for his subject were infectious. His preference was always for the small group or tutorial: large audiences made him uneasy. Students who displayed to him the qualities of integrity, so manifest in everything he did, won his friendship. A remarkable number of those who passed through his laboratory developed an enduring admiration and affection for him, expressed in the support of a memorial lectureship at Stanford in his name.

Some keep their professional and domestic lives strictly separate; not so, George Feigen. He shared with Priscilla, his wife, friend, and companion for thirty-five years, a love of young people, and so their house was frequently a meeting place for current and former students. They received a warm welcome and the opportunity to see George for what he was: not only a fine scientist, but a liberal scholar of considerable erudition and a wise counselor. He was widely read, particularly in the literature of the 19th and early 20th centuries, and in at least three languages. He had a predilection for English literature and could quote Kipling or W. S. Gilbert seemingly endlessly.

He spent two periods of leave in Oxford, England, in 1956–57 as traveling scholar of the American Heart Foundation, and in 1963–64 as a senior postdoctoral fellow of the National Science Foundation.

George Feigen was a man of great integrity. He always offered open-ended help and support to friends in need. Friendship was for him absolute: once bestowed, it was never rescinded. For many, his death has created a profound sense of loss.

Keith B. Taylor
Julian M. Davidson

Name That Physiologist Contest

Twelve members responded to the call for identification of the unknown physiologists in the collection of photographs taken in the 1940s and 1950s by Fred A. Hitchcock (*Physiologist* 27(3): 128–130, June 1984). Of those who sent in entries before the deadline, the winner, with four correct identifications, is Ralph H. Kellogg, Professor of Physiology, University of California, San Francisco. Nello Pace, Professor of Physiology Emeritus, University of California, Berkeley, upon special request, was able to name five people in the Donner Laboratory group photo (photo 15). In all, twelve of eighteen blanks were filled, at least tentatively. Most of the mystery physiologists were independently recognized by two or more persons. Two respondents were so observant as to point out an error in the contest and in the caption for photo 10. The unknown man in this photo, now identified as Hugh Van Liew, was not at the far right as stated but rather in the center. The results obtained are as follows, with the recently named physiologists underlined (the numbers refer to the photos as published in the June *Physiologist*):

3. Robert E. Swanson (University of Oregon Health Sciences Center, Portland, joined APS in 1963), M. B. Visscher.

10. Left to right: Gerald Kanter, Hermann Rahn, Hugh Van Liew (SUNY Buffalo, joined APS in 1962), Walter Massion, Michael Lategola.

14. John Paul Quigley (1896–1967, University of Tennessee, joined APS in 1929).

15. Left to right: Franklin M. Henry (Physical Education, UC Berkeley); Cornelius M. Tobias (Medical Physics, UC Berkeley); William E. Berg (Zoology, UC Berkeley); F. A. Hitchcock; unknown man; unknown woman; Lola S. Kelley (UC Berkeley, joined APS in 1956); unknown man; Enrique Strajman. The date was identified as 1946–47.

16. Left to right: unknown man; Franklin M. Henry. Photo dated 1946–47.

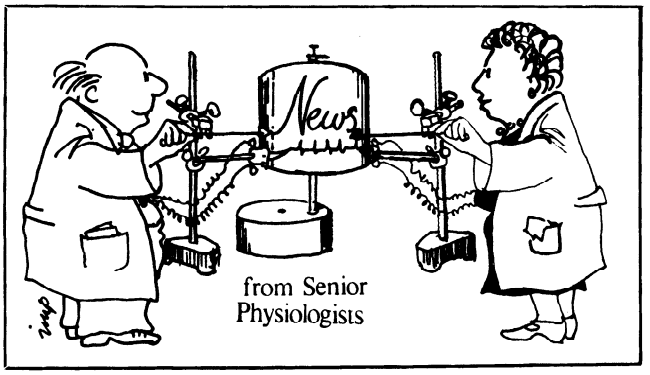
21. Left to right: Milton O. Lee; F. A. Hitchcock; unknown man.

22. Left to right: William V. Whitehorn (USUHS, joined APS in 1946); an unknown medical student subject; Abraham Edelmann (1915–1973, Westinghouse, joined APS in 1948). The date was identified as 1944–45.

Thanks to all who participated. Everyone will be sent a Centennial memento.

Future Meetings

1985	
FASEB Annual Meeting	April 21-26, Anaheim
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	



Albert S. Gordon to Bob Alexander:

I am still engaged in teaching and research in N.Y.U.'s A. S. Gordon Laboratory of Experimental Hematology, with 27 years of continuous support from the beneficient NIH. In Paris, an international conference on Regulatory Mechanisms in Hematopoiesis was recently dedicated in my honor, in addition to my previous recognitions by receipt of the A. Cressy Morrison Prize and the William Dameshek Prize in Hematology. Best regards to all my friends in APS.

New York University
100 Washington Square East, 952B
New York, New York 10003

Miriam E. Simpson to Edward Adolph:

I received your card on the day I attained ninety, and it added pleasure to the day. I must admit I consider it an achievement in spite of the general increase in longevity! It was a compliment which I appreciate to be remembered by the Committee on Senior Physiologists of the American Physiological Society.

1133 Euclid Ave.
Berkeley, CA 94708

David E. Goldman to Roy Greep:

In the seven years since I answered one of your letters there has been little change in my status. I am a part-time Guest Scientist at the NIH Biophysics Laboratory at MBL in Woods Hole. Among my projects is some collaborative research on the mechanical stimulation of the squid axon. Part time is slow work. Also, my collaborator, Jay Wells, has himself retired; nevertheless, the results are gradually being put together. We may even publish them! I have also been involved in a collaborative study of population dynamics in small mammals at SUNY Binghamton, adding systems analysis and computer simulation. In addition I get involved in community activities (arts and sciences) in a pale imitation of my wife. Occasional lecturing and consulting almost complete the picture. My wife and I love to travel and manage a trip every year or two. Is all this too much? Yes, but it's great fun. By the way, I have no interest in writing books or memoirs, nor do I have any words of wisdom to offer.

63 Loop Rd.
Falmouth, MA 07540

Mrs. Rulon Rawson to Roy:

On this cold very snowy morning I am writing to thank you for your note. Rulon was so happy to hear from you. We have had a little bad luck. He was doing so very well, walking all over with his cane, and then he fractured his hip. He has been in a great deal of pain. We talk of you many times, and Rulon gets so homesick for his Boston and New York friends. I read the *New England Journal* to him, and you should hear me pronounce the medical words. But with a little try he can always say them for me.

875 Donner Way
Salt Lake City, UT 84108

Kapp Clark to Roy:

Thank you for your note of birthday wishes. I have been retired for several years and have slowly drifted away from medical science, so that by now my interests are largely grandchildren, electric trains, very amateur astronomy, and kites. Although I still get a few scientific journals, my attention is devoted mostly to *Sky & Telescope* and *Model Railroader.* Everyone told me that I would go off my rocker if I retired early. Perhaps I have, but not because of retirement. For me it is great fun.

843 Parkes Run Lane
Villanova, PA 19085

Announcements

1985 Brookedale Awards

The Gerontological Society of America announces the 1985 Brookdale Awards for distinguished contributions to gerontology. Three awards will be given this year, each carrying a $25,000 cash prize: *1*) to a citizen of the United States for contributions to gerontology through RESEARCH in biology or clinical sciences; *2*) to a citizen of the United States for contributions to gerontology through LEADERSHIP in the social or behavioral sciences; and *3*) to a non-US citizen for contributions to gerontology through research and/or leadership. All three awards are given to gerontologists recognized both nationally and internationally for their contributions to the field. The awards will be conferred at a special ceremony during the Society's Annual Scientific Meeting in New Orleans, 22–26, November 1985. *Nominations:* Brookdale Selections Committee, c/o The Gerontological Society of America, 1411 K St., NW, Suite 300, Washington, D.C. 20005. *Deadline:* 1 June 1985.

Scientific Award 1985

The Hildegard Doerenkamp and Gerhard Zbinden Foundation for Realistic Animal Protection in Scientific Research announces a prize of DM 50,000 to be awarded for an outstanding scientific contribution to replacement of laboratory animals in teaching in biology and medicine. The applications may consist of illustrated descriptions of the procedures (teaching aids), audiovisual presentations, computer programs for simulation of animal experiments, anatomical models, etc. All materials remain the property of the applicants and will be returned within three months after distribution of the prize. The jury reserves the right to split the prize among not more than three applicants.

Applications: Professor G. Zbinden, Chairman of the Committee of Adjudicators, Institute of Toxicology, Schorenstrasse 16, CH-8603 Schwerzenbach, Switzerland. *Deadline for submission* of the *contributions:* 31 December, 1985.

Internation Symposium on Cardiogenic Reflexes

An International Symposium on Cardiogenic Reflexes will be at Bodington Hall, University of Leeds, United Kingdom, 16-20 September 1985. This symposium is being organized by the Department of Cardiovascular Studies, University of Leeds under the auspices of the Commission on Cardiovascular Physiology of the International Union of Physiological Sciences. Sessions include Electrophysiology of cardiac receptors; Cardiovascular reflexes from cardiac receptors; Effects of cardiogenic reflexes on kidney and electrolytes; Physiological role of cardiogenic reflexes; Central pathways: anatomy and electrophysiology; Central pathways: linkages; and Role of cardiogenic reflexes in disease. *Information:* Dr. R. Hainsworth, Dept. of Cardiovascular Studies, University of Leeds, Leeds LS2 9JT, UK.

Final Workshop on Animal Care and Use Committees

The Scientists Center for Animal Welfare announces the final workshop in its successful 1984–1985 series on how to run an effective Animal Care and Use Committee. The workshop goal is to identify essential functions, membership criteria, and procedures of institutional committees, and to prepare a consensus guide to effective committees. Particular focus is on animal experimentation protocol review. "Animals and the Scientist: Institutional Responsibilities" will be held May 23-24, 1985, at the Aspen Institute, Aspen, Colorado.

The workshop is aimed at current and potential members of Animal Care and Use Committees, institutional officials, research investigators, laboratory animal personnel, community members, philosophers, and students.

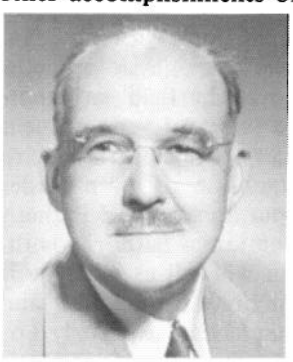
The program will include up-to-date information on current and proposed national policies concerning Animal Care and Use Committees. Speakers will include D. J. Ramsay, University of California, San Francisco, who will describe well-tested protocol review procedures and institutional policies; A. L. Caplan, Hastings Center, NY, will draw on experience gained from human experimentation committees in his address entitled "Doing Ethics by Committee"; B. Gordon, American University, Washington, DC, "Problems Faced by Small Institutions"; R. Simmonds, Uniformed Services University of the Health Sciences, Bethesda, MD, "Investigator Training; How the Committee Can Help"; H. C. Rowsell, Canadian Council for Animal Care, Ontario, "The Public Concern"; A. Flemming, Bates College, ME, "Philosophical Issues of Animal/Human Relationships", and others.

Three previous workshops in this series were held during 1984 at the Johns Hopkins University, Michigan State University, and the University of Southern California. Full proceedings of all workshops will be published as a book. This will include a consensus guide to effective Committee policies, practices and management. *Information:* Dr. F. Barbara Orlans, Scientists Center for Animal Welfare, P.O. Box 9581, Washington, DC 20016; (301) 229-8045.

The First American-Based *Handbook of Physiology*

FRANCES K. O'MALLEY AND H. W. MAGOUN
Department of Anatomy and Brain Research Institute
School of Medicine
University of California, Los Angeles
Los Angeles, California 90024

In the upcoming Centennial Celebration, the American Physiological Society may wish to include, among other accomplishments of its past quarter century, the



success of the development and publication of the *Handbook of Physiology,* initially proposed by **Maurice B. Visscher** and John Field. John Field, as Editor-in-Chief, organized and implemented the project at UCLA's new School of Medicine, with Victor Hall its hard-working Executive Editor. Over a period of three years, Victor Hall and eighty-one neurophysiologists in this country and abroad contributed time and effort to assemble the three volumes of *Section I: Neurophysiology,* initiating in 1959 and 1960 the first full-scale American *Handbook of Physiology.*

In his *History of the American Physiological Society: The Third Quarter Century, 1937–1962,* Wallace O. Fenn states (p. 77): "The *Handbook of Physiology* was first suggested by Dr. Maurice B. Visscher, a member of the Board of Publication Trustees [BPT] during the last year of this writer's term as Chairman (1955). The first steps were taken to start this enterprise the same year, including a postcard canvas of the membership, which was overwhelmingly in favor of the undertaking. As Chairman [of BPT] from 1956 to 1959, Dr. Visscher organized the necessary editorial boards and continued as chairman of the Handbook Committee. . . . The first section of the *Handbook* was the Neurophysiology Section, published in three volumes, with John Field as Editor-in-Chief, H. W. Magoun as Section Editor and Victor Hall as Executive Editor. . . ."

A second, more extensive account of this development recently came to light when Stephen Geiger retrieved from publications files a two-page typed draft prepared by the Publications Office, probably in 1959. This valuable previously unpublished account presents a timetable of the Handbook's development starting two years earlier than Fenn's and, in general, is more authoritative.

We are deeply indebted to Toby A. Appel, Historian/Archivist of the American Physiological Society, for her cordial provision of records of the Board of Publication Trustees and other material relating to the publication of the *Handbook of Physiology.*

Handbook of Physiology Brief History of the Early Years

"The idea of a multi-volume *Handbook of Physiology* originated with Dr. M. B. Visscher. In November 1953, Dr. Visscher put his thoughts in writing to Dr. W. O. Fenn, Chairman of the Board of Publication Trustees, suggesting that a *Handbook* series be presented for consideration at the next meeting of the Board. The nucleus of the proposition was that the Board of Publication Trustees should 'undertake to edit and publish over the next 5 or 10 years a multi-volume *Handbook of Physiology* which would be a somewhat streamlined version of the Bethe *Handbook* series developed before the war in Germany.'

"In December 1953, the BPT sent a questionnaire postal to present and former Council members and other selected consultants of the Society, asking for suggestions and comments on the proposed publication. The covering letter stated that the *Handbook* should be as 'advanced in its analytical treatment as it is possible to make it. Thereby it will serve as a guide to future investigators as well as a reference book for past work. The articles should differ from monographs in that they would not stress the work of a particular school to the exclusion of others. They would differ somewhat from *Physiological Reviews* articles in that they would not try to cover all the papers published in the last ten or more years, good or bad, but would try to give a well-balanced appraisal of the facts and principles so far established, not neglecting, however, both sides of controversial topics with the conflicting evidence as it now exists. It would presumably be restricted at first to a complete coverage of vertebrate physiology but might be extended in later volumes.'

"On the preliminary mail vote, there was not unanimity on the plan of separate *Handbook* volumes; so in March 1954 the BPT sent out a second questionnaire to 71 physiologists in the U.S. and abroad suggesting, as an alternative to the volumes, supplements to issues of *Physiological Reviews*—in effect, each supplement would represent a chapter in a *Handbook of Physiology,* and over the years the whole field of physiology would be covered 'as thoroughly as possible with a comprehensive and authoritative presentation of the subject to supply the needs of advanced students in the field.' If the *Physiological Reviews* plan was accepted, it was proposed that the supplements be paged to fit into different volumes, e.g., Circulation volume, so that they could be purchased separately as desired. Replies were received from 49 physiologists, including 18 foreign correspondents: 38 were in favor of the supplement to *Physiological Reviews;* 2 favored the original *Handbook* plan; 4 voted both proposals a waste of time; 6 had intermediate opinions.

"During 1954, Dr. Visscher, Chairman of the ad hoc committee on the *Handbook,* recommended to Council

that a pilot volume be prepared as a supplement to *Physiological Reviews* and Dr. John Field was asked to serve as chairman of an editorial board to secure manuscripts designed to cover the field of neurophysiology.

"At the 1955 annual meeting in San Francisco, the Board of Publication Trustees agreed to sponsor the *Handbook* project and authorized Dr. Field to proceed with the collection of manuscripts for two or three volumes at a cost not to exceed $10,000 over a period of three years. The exact medium of publication was to be explored at a later date when most of the manuscripts were in hand. At this meeting the Publication Trustees appointed an editorial staff for the project, consisting of Dr. Field as Editor-in-Chief, Dr. Victor E. Hall, Executive Editor, and Dr. Horace W. Magoun, Section Editor in Neurophysiology.

"During 1958, the decision was made to issue the *Handbook* in separate volumes – not as supplements to *Physiological Reviews*; manuscripts for volume I, *Neurophysiology,* were in to the printer; manuscripts for volume II, *Neurophysiology,* were in the editorial office and in process. Williams and Wilkins was selected as commercial distributor of the volumes. . . ."

The Publication Office's date of Visscher's proposal of a *Handbook of Physiology* as November, 1953 is supported by minutes of the Board of Publication Trustees meeting on November 15, 1953, at which Visscher was quoted: "A new publication venture is what we need. . . . A Physiological Handbook, for example. . . . There is a great need for such an enterprise to keep us from stagnating."

The Office's account of the second 1954 questionnaire is supported by the Report of the Board of Publication Trustees to the APS Council in April, 1954. Under the heading "Handbook or Supplement to Physiological Reviews," the reaction to the proposal that the Society undertake the publication of a *Handbook of Physiology,* or that supplements to *Physiological Reviews* be published which would eventually contain sufficient material to make a handbook, was determined by asking 70 people in America and abroad. The responses were overwhelmingly in favor of the latter, i.e., publication in *Physiological Reviews.* After extended discussion, it was decided that a special committee be appointed by the BPT to study the problem and present a prospectus or outline of what was envisioned.

Visscher, in his enterprising manner, promptly took steps to assemble such an ad hoc committee and, on May 24, 1954, wrote Fenn: "As you will note from the enclosed. . . , John Fulton has declined membership on our ad hoc Committee . . . since it will involve travel. The problem now arises as to another person in his place. I have not yet heard from John Gray . . . [Ancel] Keys and [John] Field have agreed to serve. . . . we should have as strong a committee as possible because the venture we are discussing is unconventional and would have to have strong backing in order to be accepted with enthusiasm. . . ."

This was the first mention of John Field in the context of a prospective *Handbook of Physiology.* It was succeeded by a succession of communications among the members of the BPT. On December 11, 1954, Fenn wrote:

"You will recall that I was authorized to talk to John Field concerning an editorial board for a *Handbook.* I did discuss the matter with him at Madison and he gave me a tentative acceptance. We agreed that he would write me a letter outlining his detailed plans and particularly his financial requirements for this program. I have not heard anything from him since that time, but I have already written to him asking for some further report.

"It is perhaps a little premature to discuss a publisher at this time but we should have some long range plans about the publication of this particular volume or chapter after John Field gets it finished. It should be so arranged that it can fit into a more extensive series if that turns out to be desirable. It hardly seems to me possible to include the whole publication as a supplement to *Physiological Reviews* but this is certainly one of the alternatives."

On February 1, 1955, Visscher replied:

"There is only one important reason in my mind for having a meeting of the board with Dr. Field before the San Francisco meetings. That reason is that if we are to proceed, it would be very helpful for Jack Field to be able to arrange beforehand for meetings in San Francisco with prospective authors for the *Handbook* material. I think it might save nearly a year of time in preparation if he had such an opportunity. This could hardly be done on the spur of the moment in San Francisco. He would have to have opportunity to correspond beforehand."

On February 10, 1955, Hallowell Davis wrote to Fenn:

"I also have received the latest neurophysiology outline from John. It seems to cover the field very thoroughly and to have lined up a series of very eminent prospective authors. It will be a terrific editorial job to get them all to sign on the dotted line and even harder to get them to deliver their output on schedule. Perhaps hardest of all will be the coordination of authority within a given section. I hope John will tell us what he is expecting the various 'introductions' to be like and whether the authors of these chapters are expected to be captains of the teams that write the chapters they are introducing. I imagine this is not the case because I note that this is where most of the foreign neurophysiologists seem to turn up. All of this will be an interesting venture in organization as well as an assembling of information."

On September 6, 1955, at a meeting of BPT at the APS Fall Meeting at Tufts University, Field summarized progress:

"*a*) Horace W. Magoun, Section Editor in Neurophysiology, has written to 20 sub-editors and writers; *b*) outlines have been requested but none has been received; *c*) eight of the twelve individuals asked to prepare introductory chapters have accepted; *d*) approximately 25 pages have been allocated to each author, although several may need more space, e.g., John Fulton may want 150 pages for the history of neurophysiology[1]; *e*) the *Handbook* will be published in volumes, not in fascicles, and the first two volumes will be experimental; *f*) the deadline for completion of the first volume is August 1956; *g*) a definite decision has not been made on the format; however, authors have been told that it will probably be similar to that of *Physiological Reviews.* Dr. Field asked that the Editorial Office send direct to Victor E. Hall, Executive Editor, details on mechanics (use of symbols and abbreviations; lettering for graphs;

[1] An historical introduction was eventually written by Mary A. B. Brazier.

degree of anatomical detail necessary in photomicrographs; amount of laboratory jargon acceptable; list of publications as models of style, e.g., *Handbook of Experimental Psychology*). The Editorial Office will send a check to Dr. Field for setting up a petty cash account for *Handbook* supplies; the Board authorized him to purchase a typewriter and have stationery printed, sending bills to the Society Central Office for payment."

Following this up, on September, 21, 1955, Field sent Visscher, Chairman of BPT, a more extended report showing that as a result of first series of invitations to contributors, there were 34 acceptances and 7 refusals. "Dr. Hall reports that this is a much better accept/refuse ratio than the *Annual Review of Physiology* gets from its invitations. In general, those who have accepted seem to be enthusiastic about the project although modest about the possible value of their own contribution. It is our view that much of this success is due to the drawing power of the Section Editor, H. W. Magoun. Enclosed please find sample letters of invitation to (1) Authors of introductory section and (2) chapter authors. Both sets were signed by Magoun. These letters serve as invitations and also set forth our concept of the scope and purpose of the *Handbook*."

A final obstacle to publishing a *Handbook of Physiology* under this title was overcome at the meeting of the BPT at Beaumont House in December 1958. Visscher "reviewed the reasons why it had been decided by the members of the BPT and the Managing Editor [Milton O. Lee] that the name of the *Handbook* be changed to *The Physiological Sciences*." It was thought that the name handbook, "carried a connotation not compatible with the work itself." Works such as the *Handbook of Biological Data* gave people the wrong impression of the project underway. However, Visscher reported that after the Board had agreed several months back to change the name of the series to *The Physiologcial Sciences,* Field had "taken violent exception to a change being made, stating that reference to the *Handbook of Physiology* has already been made in literature now being printed." Visscher admitted that BPT "had erred in changing the name without consultation with the Editors of Section I" and suggested that the subject be discussed further and a definite decision be made.

William F. Hamilton recalled that he had always been dissatisfied with the title *Handbook of Physiology* and preferred instead that the term "Foundations" be included in the title. He particularly liked the title, *Foundations of Physiology.* Hallowell Davis favored the title *Handbook of Physiology* and cited as precedents the *Handbook of Speech Pathology* and *Handbook of Physics.* Visscher pointed out "that at the time he had favored *The Physiological Sciences* as a title, there was some consideration to inviting the sponsorship of the International Union of Physiological Sciences for Section II, and the fact that the proposed title of the series coincided with the name of the Union seemed desirable."

Four titles were then considered: Foundations of Physiology, The Physiological Sciences, Handbook of Physiological Science, and Handbook of Physiology. Finally, Hamilton suggested that the title be changed back to *Handbook of Physiology,* but with a descriptive subtitle added. The motion was carried and it was decided that the subtitle on the title page should read, "A critical comprehensive presentation of physiological knowledge and concepts."

The Editor-in-Chief of this first American *Handbook,* **John Field,** was born in Philadelphia in 1902 into

a family of prosperous merchants. He began education in the Penn Charter School, graduating in 1919. His mother's doctor then advised them to move either to California or Switzerland, since John had suffered from pneumonia every winter. They chose Palo Alto, California, and John entered Stanford there in 1919. Majoring in chemistry, he obtained an A.B. in 1923 and continued graduate study in biochemistry under Carl Lucas Alsberg, then Director of Stanford's Food Research Institute and Dean of Graduate Study. Gaining his Ph.D. in 1927, John became a member of Stanford's faculty and was made Professor of Physiology in the Medical School in 1941. In 1948, he made several trips to the Arctic Research Laboratory established by the Office of Naval Research [ONR] at Point Barrow, Alaska, and, on leave, in 1949–50 moved to Washington in the Biology Branch of the ONR. In 1951–52 he became Associate Director of Medical and Biological Sciences in the National Science Foundation and, in absentia, was appointed the founding chairman of the Department of Physiology in the new School of Medicine at UCLA.

Field was well known to Visscher and to the staff of APS. When he moved to UCLA, he had brought with him his associate, Victor Hall, Editor of the *Annual Review of Physiology* at Stanford and Victor brought the *Review's* office as well. This publication was then jointly sponsored by APS and *Annual Reviews.* Visscher had served on the *Annual Review's* Editorial Committee from 1949 to 1954, and Field from 1952 to 1962. They had been associated in this activity, therefore, during 1952, 1953, and 1954, the critical years in initiating the *Handbook of Physiology.* Moreover, during 1949–52, when John Field was on leave in Washington, DC, the offices of the American Physiological Society were still on DuPont Circle, in downtown Washington, preceding their move to Beaumont House, Bethesda, in August, 1954. During his stay John was a member of the Cosmos Club, in that period the eating and meeting place of scientists in Washington and just two blocks from DuPont Circle. It is highly likely that sociable John Field maintained some contact with his peers in the American Physiological Society's office in Washington during 1949–52.

It is Mrs. Sally Field's recollection that John Field had himself first proposed the preparation of a *Handbook of Physiology* in response to a request or questionnaire from the Washington Office, preceding those mentioned above, asking for suggestions on how to spend constructively the rapidly mounting publication reserve fund. Unfortunately, records of this request are not available and its date is uncertain, but Mrs. Field can still vividly recall John's excitement at the prospect of preparing a *Handbook of Physiology.*

There is no question concerning the problem of the publications reserve fund, however. In his *History* (p. 45), Fenn quotes from a letter of Hallowell Davis: "In 1954, I became a member of the Board of Publication

Trustees. Here at last, I got some real insight into the financial operations. . . . We had begun to be embarrassed by the increasing accumulation of the fund and possible difficulties with the Internal Revenue Service. It was partly to avoid too rapid further accumulation that the *Handbook of Physiology* was initiated. I believe, in retrospect, that the *Handbook* has proved to be one of the major contributions of the Society to physiology, and at the same time, it has established a unifying source within the Society, as a visible symbol of something we have done and continue to do together."

The elegance of John Field's preface, opening *Section 1: Neurophysiology,* published in 1959, demonstrated his familiarity with the historical development of *Handbooks* and identified him as an ideal person to guide the preparation of the first three volumes. His preface began:

"This *Handbook of Physiology,* like its predecessors from von Haller on, is designed to constitute a repository for the body of present physiological knowledge, systematically organized and presented. It is addressed primarily to professional physiologists and advanced students in physiology and related fields. Its purpose is to enable such readers, by perusal of any Section, to obtain a working grasp of the concepts of that field and of their experimental background sufficient for initial planning of research projects or preparation for teaching. . . .

"This *Handbook* stands as the current representative of an historic series of efforts to collect and systematize biological knowledge—a series continued when the Board of Publication Trustees of the American Physiological Society decided in 1953 to sponsor the present undertaking. . . ."

Field traced the history of handbooks of physiology from as far back as a Sumerian pharmacopoeia of 2100 B.C. Although he included among "notable examples of handbooks," the assembly of differently authored chapters in E. A. Shafer's *Textbook of Physiology* published in Edinburgh and London in 1898–1900, he, surprisingly, made no mention of a very significant precedent, *An American Textbook of Physiology,* edited by William Henry Howell, and first published in Philadelphia in 1896. Howell, Professor of Physiology at Johns Hopkins, was President of the American Physiological Society for six successive terms beginning in 1905. The *American Textbook's* revised Volume II, published in 1901, was more than 500 pages long and devoted principally to neurophysiology. Its four authors were among the American elite in that field and time. Its first section on "General Physiology of Muscle and Nerve, and Locomotor Mechanisms" was prepared by Warren P. Lombard, Professor of Physiology at the University of Michigan. The second section on "Central Nervous System" was prepared by Henry H. Donaldson, then Professor of Neurology at the University of Chicago. The third section on "Special Senses and Muscular Mechanisms" was prepared by Henry P. Bowditch, Professor of Physiology at Harvard Medical School and Henry Sewall, Professor of Physiology at Denver College of Medicine.

In his preface Howell stated: "An earnest effort has been made to render this book a reliable repository of the important facts and principles of physiology and, moreover, to embody in it the recent discoveries and tendencies that have characterized this science within the last few years." Although ostensibly prepared for medical students, it was "hoped that the book will be found useful to many practitioners of medicine who may wish to keep in touch with the development of modern physiology. For these reasons, references to the literature [which had been included] are not only valuable, but frequently essential." Although John Field may not have considered this *American Textbook of Physiology* "a notable example of a handbook," as an early American harbinger in this direction, it deserves recognition here.

Also omitted by Field was an indubitable American handbook that was even titled, *Handbook of Physiology.* It was "revised and rewritten by Charles Wilson Greene, Professor of Physiology and Pharmacology at the University of Missouri" and published in New York in 1925. Greene had been Secretary of APS for nine years and was its 14th President, in 1934. His handbook was, however, not original but actually the "Tenth American Revision" of Kirkes' *Handbook of Physiology,* a popular 19th century English textbook that had gone through myriad editions abroad.

The Executive Editor, **Victor Hall** and his Assistant, Mrs. Sally Field, were the hardest working members on the APS Handbook project.

Victor Hall was born in Victoria, British Columbia. After his college study at the University of California, Berkeley, he entered Medical School at Stanford and, awarded his M.D. in 1929, was appointed assistant professor of Physiology. In 1932, James Murray Luck, professor of chemistry at Stanford, initiated the *Annual Review of Biochemistry.* This was such a success that, in 1938, he discussed with BPT the idea of starting an *Annual Review of Physiology.* This was approved with Luck, Editor, Hall, Associate Editor, and an Editorial Committee appointed by APS, which chose the topics and authors for each edition. Victor was made Editor in 1947 and, on moving to UCLA in 1951, continued in this role by communicating via mail with the staff of the *Annual Review's* Office in Palo Alto.

When Victor was appointed Executive Editor of the *Handbook of Physiology* in 1955, he had completed some fifteen years of familiarity with and experience in determining physiological topics, selecting authors to prepare chapters on them, and editing and arranging their contributions for publication. In short, the *Handbook* project was initiated with the blessing of a talented, experienced and, in the best sense of the word, a professional Editor—with the marvelous personality, as described by Magoun, of a "sweet-blooded" man.

In recalling his role in preparing the volumes on neurophysiology, Victor began[2]: "This was all started by Dr. John Field. The American Physiological Society's Board of Publication Trustees had accumulated a considerable sum of money in excess of the cost of the journals they were publishing and was seeking some good way to spend it. Dr. Field, who was acquainted with the nineteenth century German Handbücher, which did such a magnificent job for their time, suggested to

[2]Oral History Program, Brain Research Institute, UCLA, 1980.

the committee that it support the preparation of a contemporary, multi-volumed, American-based *Handbook of Physiology.* Moreover, he volunteered, on behalf of himself, me, and Dr. Magoun, to attempt production of the first three volumes of this extended undertaking on *Neurophysiology.*

"The proposal was approved by the Board in 1953 and I was made Executive Editor, which meant that I did all the work, except that in making overall policy. Dr. Magoun and I worked out a list of subjects and called a meeting of BRI members and others interested in neurology to draw up a list of chapters and authors. From this, Magoun and I made a preliminary list, approved by the group, which then proceeded to add the names of authors, here or elsewhere, suitable for writing the chapters. A final meeting, held at Dr. Magoun's house, was completely successful. So I had my 'sailing orders' and drew up a letter, which Dr. Magoun signed, inviting the authors selected to do this job.

"This was to be a sort of super-textbook and I set up an office for its preparation, with Mrs. Sally Field, who was a wonderful person, my assistant for this job. We sent letters to all the authors and provided guidance for those with problems. I also served as editor of this work, reading the manuscripts as they came in and they started coming in about a month after we sent out the invitation. I made the changes I thought were needed in the manuscripts and returned them to the authors for revision, if they agreed. We never disagreed with any author, and whatever they replied, we sent off to the American Physiological Society's Washington office, which handled the publication side of the project. This was a big job and we were working on it for about three years. With respect to the Society's goal of spending the money they had accumulated, however, the *Handbook* project was a total failure! Instead of getting rid of money, the *Handbooks* were so popular that the Society only added to their funds, as it went on with additional volumes, which other persons took over. I was responsible for only the first three volumes, which have been a tremendous success. This is the story of the *Handbook of Neurophysiology* and I consider it one of my major successes."

Epilogue: The Second Edition of the *Handbook of Physiology*

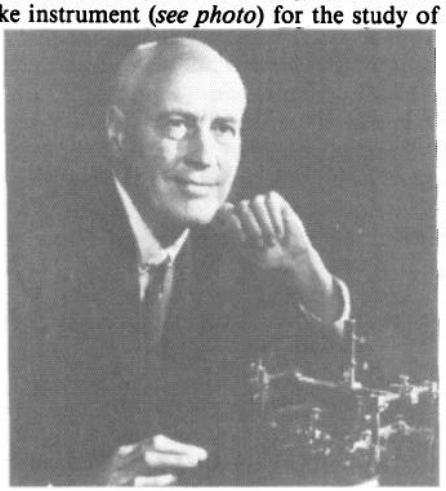
A little more than twenty years after its first edition in 1959–60, in 1983 the second edition of the *Handbook of Physiology* has begun publication by the American Physiological Society. Like the first, the second edition's *Section 1* is devoted to the nervous system. Moreover, its two Section Editors, John M. Brookhart and Vernon B. Mountcastle, had each contributed papers to the maiden publication.

There the analogy ends, for the present *Volume I: Cellular Biology of Neurons* (1,238 pages), edited by Eric R. Kandel, is devoted to the scope, direction and excitement of research in modern cellular neurobiology. *Volume II: Motor Control* (1,548 pages), edited by Vernon B. Brooks, covers the concepts and analyses of motor control from automative unconscious adjustments to voluntary conscious movements and behavioral performance. *Volume III: Sensory Processes* (1,244 pages), edited by Ian Darian-Smith, presents a comprehensive account of current knowledge of the neural mechanisms used to sense the outside world.

The 4,030 pages of these three volumes are already more than double the less than 2,000 pages of the first edition's three neural volumes. *Volume IV: Intrinsic Regulatory Systems of the Brain,* edited by Floyd E. Bloom, is nearing completion. Two additional volumes, one on higher functions of the nervous system edited by Fred Plum and the other on development of the nervous system edited by Maxwell W. Cowan will conclude the section. Clearly, the physiology of the nervous sytem is still an expanding field.

H. W. Magoun

Horace W. Magoun was born in Philadelphia but grew up a New England boy. After college at the University of Rhode Island, he started west to gain a master's degree at Syracuse with a thesis on the Mauthner cells in the brain stem of Petromyzon. Continuing west, he gained a Ph.D. at Dr. S. W. Ranson's Institute of Neurology at Northwestern University Medical School in Chicago and stayed on until midcentury. Ranson had just revived the Horsley-Clarke instrument (*see photo*) for the study of the brain stem of the cat and monkey. After Magoun had become familiar with the intricacies involved, he spent most of his time guiding Ranson's doctoral students and postdoctorals in their experiments. When Ranson had visitors, however, he would always bring them into the laboratory and say, "Now this is the Horsley-Clarke instrument and this is Dr. Magoun!"



Following Ranson's demise, Magoun moved into the Anatomy Department of Northwestern University Medical School and continued to pursue collaborative research, but now with Warren S. McCulloch and others at the Illinois Neuropsychiatric Institute and with Donald B. Lindsley in the Psychology Department of Northwestern and Guiseppe Moruzzi, visiting professor for a year from the University of Pisa, Italy, all of whom were exploring functional relationships between the brain stem and cerebral cortex.

In 1950, Magoun's westward trek reached its end by his joining, as Professor of Anatomy, the faculty of a new School of Medicine at the University of California, Los Angeles. After several years of effort and development, in 1959, John D. French, Donald B. Lindsley, Magoun, and many others established a Brain Research Institute at UCLA. In October 1984, this Brain Research Institute celebrated its 25th Anniversary, in connection with which French, Lindsley, and Magoun have just published *An American Contribution to Neuroscience: The Brain Research Institute, UCLA 1959–1984.*

Letter to the Editor

The Teaching Hour/ Course Duration Ratio

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In the construction of a medical curriculum, the number of teaching (contact) hours is an element that is always considered because the total number of available contact hours is finite and there must be a guide to allow for the fitting of various subjects into the limited time frame. Indeed, the American Association of Medical Colleges Curriculum Director (12th ed., 1983-84) provides a listing of such contact hours for accredited medical schools in the United States and elsewhere. On the other hand, an important parameter for a medical curriculum—the concentration of subject matter relative to time—has been ignored. Thus two schools may each allocate, for example, 170 contact hours to physiology, but one school may disperse that time over an entire academic year, whereas the other school may wedge the hours into 8 or 9 weeks. To make a hasty assessment of the relationship between the physiology course length and the number of contact hours in physiology (i.e., lecture density and total contact hour density), I used the above-mentioned Directory for contact hour data and then interrogated Physiology Departments as to course length.

Of 127 schools in the continental US, 27 were eliminated from further consideration because the Directory data did not disclose any discrete definable physiology course; in most of these instances, an organ-systems approach was indicated. A questionnaire simply requesting course length was answered by 91 schools and not answered by 9 schools; in some instances the respondents volunteered contact hour data, which permitted an updating of the Directory information. Of the 91 schools providing information, 34 offered a "Full" or traditional physiology course, and 57 presented a "Partial" course in which neurophysiology was relegated to a neuroscience course.

Table 1 is derived principally from the Directory data and summarizes the number of contact hours in physiology for those schools offering the "Full" or the "Partial" course. Median values are shown as well as those for the 1st and 3rd quartiles, which represent the values for the 50% of the schools surrounding the median.

Table 1

Type of Course	Total Lecture, Hours	Total Contact, Hours
"Partial"	88 (77-100)	153(123-175)
"Full"	112 (89-136)	184 (151-202)

It is evident that the average "Partial" course has some 24 fewer lectures and 31 fewer total contact hours than the traditional "Full" course. The neuroscience courses offered in conjunction with the "Partial" physiology courses had an average of 60.8 lecture hours, and it is therefore likely that the "lost" 24 contact hours were neurophysiology lecture hours that have simply been shifted into the neuroscience courses, where they represent about one-third of the neuroscience lectures.

Table 2

Type of Course	Course Duration, Weeks	Total Lecture Hours/Week	Total Contact Hours/Week
"Partial"	17.0 (15-21)	5.0 (4.2-6.0)	9.0 (6.8-10.7)
"Full"	18.5 (16-22)	5.4 (4.4-8.0)	9.5 (6.6-10.9)

In Table 2 the element of course length is introduced as well as the concept of the number of contact hours per week. The median course length for the "Partial" and "Full" courses was equivalent to about one semester, but this value is highly misleading, since it masks an extremely wide range of course lengths and obscures the fact that the frequency distribution of course lengths is multimodal, reflecting the several types of course segments (quarters, one semester or two quarters, and two semesters or three quarters). The range of course durations was 12-40 weeks for the "Full" courses and 9-32 weeks for the "Partial" courses.

Regardless of whether the traditional course or the truncated course is offered, the average concentration of contact hours is quite similar. The median number of lecture hours per week is about 5, and there are about 4 additional hours per week devoted to labs, conferences, etc. Not shown in Table 2 but of interest is the fairly wide range of lecture and total contact hour densities. In both the "Full" and "Partial" course categories the lecture hours per week ranged from about 2.5 to 10.5 hours/week, whereas the total contact hours per week ranged from 3.5 to 19.5 hours/week.

As one might expect, there is a positive correlation between the number of contact hours and either the duration of the course or the number of contact hours per week. Nevertheless, this association is only moderate (Spearman coefficient R ranged from 0.46 to 0.63) between the number of contact hours and the contact hour per week and lower yet (R = 0.04 to 0.39) between the number of contact hours and the course durations. It is therefore reasonable to say that the teaching hour density is not merely a reflection of the number of contact hours in the course. What significance a high or low contact hour/week ratio may bear on learning effectiveness is indeed complicated by the fact that more than one course is usually offered in the same time segment of the year. It might be of interest if one could ascertain whether there is any correlation between the teaching hour density and some objective measure of performance, such as perhaps the National Board examinations.

I am grateful to all the Chairmen of the Departments of Physiology who responded so promptly to my inquiry.

Correction

Physiologist 27(6): 418, 1984. Cell and General Physiology Section Secretary is Caroline Pace.

Elementary Hemodynamic Principles Based on Modified Bernoulli's Equation

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The purpose of this article is to develop and expand the basic concepts of Bernoulli's equation as it applies in a general way to vascular hemodynamics, bearing in mind that it is only an approximation. Various simple models will be used to illustrate these concepts, and terms will be introduced and defined which are considered more descriptive and appropriate than some traditional terms.

Pressure in the vascular system is often described as hydrostatic, e.g., capillary hydrostatic pressure. This terminology is inappropriate, since it suggests pressure of nonmoving (stationary) liquids and therefore had better not be used to refer to the lateral pressure of moving liquids (which will be defined later).

The origin of pressure gradients in vertical columns of *liquids at rest* in open containers is the force of gravity acting on the particles of the liquid that bear the weight of those above. The magnitude of this pressure (P) varies with the density of the liquid (ϱ) and the height of the column (h) from a given reference plane. It is calculated by multiplying the density of the liquid by the height of the column and the acceleration of gravity (g). The latter varies with the altitude above sea level, but the difference is relatively slight within the range of altitudes inhabited by man (at sea level = 980 cm/s^2). Thus $P = \varrho gh$, where P is in dyn/cm^2 in cgs or newtons/m^2 in mks (= Pascal), ϱ is in g/cm^3 in the cgs system or kg/m^3 in the mks system, g is in cm/s^2 in the cgs system or m/s^2 in the mks system, and h = cm in cgs, or m in mks.

Since the origin of this pressure is the force of gravity, I propose to call it the *gravitational pressure.*[1] Further justification for this term is that it is universally applicable to pressure exerted by all states of matter—solids, liquids, and gases. An example of the latter is the atmospheric pressure.

[1]Traditionally it has been called hydrostatic pressure. However, since this pressure is exerted also on vertical columns of *moving* liquids it is preferable to describe it as gravitational pressure.

Let me take the problem of the mechanics of flow of liquids (commonly called "hydraulics"), which is a very complex subject, and consider it in a simple nonmathematical manner. I will confine the discussion to Newtonian liquids (incompressible) that flow in a *steady* and *streamline* or laminar manner. Here, particles of the liquid move after each other in the same path as the preceding. No two streamlines can cross one another. This is in contrast to turbulent flow in which the velocity vector varies in the transverse direction, forming eddies or vortices. A useful treatment of *steady streamline* flow was carried out by a member of a famous Swiss family of mathematicians. Daniel Bernoulli (1700–82) had a medical degree and taught in Basel, publishing his studies in a book entitled *Hydrodynamica* (1738). Bernoulli considered, for simplicity, liquids that are *nonviscous* (called "ideal") in which *frictional loss of energy during flow does not occur.* According to this concept, when such "ideal" liquids flow through a conduit in a steady manner the *total energy of the liquid* (E) remains constant at all points along the length of the conduit. There are three major components that contribute to the total energy of a nonviscous liquid per unit volume. These are *1*) pressure energy per unit volume, *2*) gravitational potential energy per unit volume, and *3*) kinetic energy per unit volume.

Pressure Energy

Pressure is defined as the force exerted per unit area of a surface ($P = F/A$). In a liquid, the product of pressure (P) and volume (V) represents the pressure energy content of that volume. In other words, PV indicates the work that has been done in imparting such energy ($PV = F/A \cdot V$ = force × distance). The units of energy are ergs (cgs system) or joules (mks system). In the original Bernoulli equation which considered *frictionless liquids,* P is the gravitational (hydrostatic) pressure of the liquid and/or the pressure derived from the conversion of kinetic energy. Unfortunately, in physics texts this is not clearly stated. Ordinarily, most pressure measurements in biology and engineering are made against atmospheric pressure as the zero reference. If atmospheric pressure is added or is included, one obtains what is called the *absolute* pressure, which would be the pressure exerted against absolute vacuum.

Gravitational Potential Energy (Potential Energy of Position)

This is the potential energy of a volume of liquid due to its position in relation to the center of the earth (*positional energy*). The further away it is from the center of the earth, the more gravitational potential energy it contains because work must be done to move it away from the gravitational pull of the earth. If such liquid is allowed to fall to a lower level it can do work or provide energy in one form or another (e.g., hydroelectric power generation, watermill). The same principle applies to solids that are located at higher levels and fall if not supported.

The gravitational positional energy of a volume (V) of liquid is equal to $\varrho gh \cdot V$.

Kinetic Energy

As is well known in physics, kinetic energy (KE) of a volume (V) of liquid that is in motion is

$$KE = \tfrac{1}{2}mv^2 = \tfrac{1}{2}\varrho V \cdot v^2$$

m is the mass of liquid ($= \varrho V$) and v is the mean velocity of flow.

Adding the above three components of energy of a liquid, we obtain the *total energy of a volume of liquid*

$$E = [P + \varrho gh + \tfrac{1}{2}\varrho v^2]V \qquad (1)$$

According to the original Bernoulli equation, in a *nonviscous* liquid that is flowing *streamline* and *steadily* in a system, the total energy per unit volume at point 1 is equal to the total energy at point 2, is equal to the total energy at point 3. Thus

$$[P_1 + \varrho gh_1 + \tfrac{1}{2}\varrho v_1^2]V = [P_2 + \varrho gh_2 + \tfrac{1}{2}\varrho v_2^2]V = \ldots \qquad (2)$$

The positions, 1, 2, 3, are arbitrary and can be any point(s) along the flowing system. The reference plane from which h_1, h_2, . . . are measured is also arbitrarily chosen.

Incompleteness of Bernoulli's Equation

The important drawback of the original equation of Bernoulli is that it was applied for liquids that were considered *nonviscous* and frictionless. Obviously, *real* liquids are viscous and "*lose energy*" under conditions of steady flow, particularly when flow is through narrow tubes such as blood flowing through the microvascular systems, e.g., arterioles and capillaries. The viscous "loss" of energy is in the form of frictional heat, which is partly dissipated to the surrounding media (e.g., pipes, vessels). This energy loss may be small or large depending on the hydraulic circumstances in a particular system. The thermal energy derived from friction is considered "lost" because it cannot be reconverted into pressure energy or kinetic energy of flow. Hence it is not included in total energy causing flow.

To modify the original Bernoulli equation so as to apply it to "real" liquids flowing streamline and steadily one must add to the equation the *thermal* (or *internal*) energy (U) of a unit volume of liquid ($U \cdot V$). More importantly, one must distinguish two possible sources of pressure when viscous liquids are pumped *through conduits.* One source is the pressure developed against the viscous resistance of the conduit. We will call it the *viscous flow pressure* or frictional flow pressure (traditionally called hydraulic pressure). For the sake of brevity, and since all liquids are viscous, henceforth we will often refer to this as the *flow pressure.* The second source is the *gravitational pressure* defined earlier.

Thus the Bernoulli equation may be modified for *viscous* liquids as follows.

at any point total energy of liquid per unit volume (E)	=	pressure energy (P • V)	+	gravitational positional energy ($\pm \varrho gh \cdot V$)	+	kinetic energy ($\tfrac{1}{2}\varrho v^2 \cdot V$)	+	thermal energy ($U \cdot V$)	(3)

viscous flow P ($\alpha \dot{Q} \cdot R$) gravitational P ($\pm \varrho gh$)

where $\dot{Q}$ is the flow rate and R is the resistance to viscous flow.

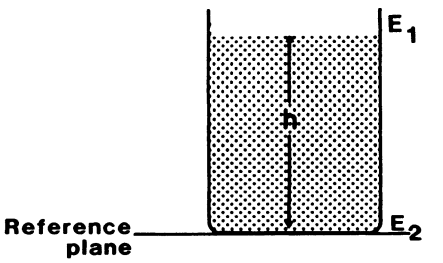
Breakdown of Components and Definition of Terms in Modified Bernoulli's Equation

Total energy gradients (excluding thermal) that cause flow of liquids may be induced by gravity or by the compression of a pump.

Gravity will induce flow of a liquid in an open container whenever the liquid is not *supported* by an opposing force anywhere *below* its exposed surface. This is based on the physical principle that liquids (as well as solids) *seek a lower level of gravitational potential energy unless supported by an opposing force.* In liquids the opposing force is normally a solid surface that contains the liquid.

Let us first apply the Bernoulli equation to the case where a liquid is contained in a vessel and *supported* at all points so that it cannot run to a lower level of gravitational potential energy (Figure 1). The gravitational *pressure energy* at the bottom is $\varrho gh \cdot V$ and at the top is zero (atmospheric pressure). On the other hand, one must also consider the gravitational *positional energy* of the liquid due to its vertical distance from the center of the earth (second term in *Eq. 3*). In this case, the liquid at the bottom has a positional energy taken to be a certain value, X (reference level) and at the top it is $X + \varrho gh \cdot V$. The sum of the two energies at the bottom and at the top has the same value. Likewise, the liquid at all levels between the bottom and the top has the same total energy. Since there are no gradients of total energy, there is no flow. Obviously, it is assumed that the temperature (or internal energy) is uniform throughout the liquid. If the liquid at the bottom is heated, its energy content increases and flows upward.

Next, let us consider the case where gravity causes flow. Figure 2 shows a reservoir from which liquid runs streamline by gravity through a horizontal rigid tube of uniform diameter to a *lower level of gravitational potential energy.* The various components of energy of the



Gravitational pressure E = 0 (atmospheric)
Gravitational potential E = X + ρgh•V
Thermal E = UV
Total E_1 = X + ρgh•V + UV

Gravitational pressure E = ρgh•V
Gravitational potential E at reference plane = X
Thermal E = UV
Total E_2 = X + ρgh•V + UV

Figure 1
Diagram to explain why a liquid in a container does not flow from a higher pressure at the bottom to a lower pressure at the top. Flow is dependent on *total* energy gradients, and with the use of the modified Bernoulli equation it can be shown that there are no total energy gradients caused by the action of gravity (provided temperature of liquid is uniform throughout).

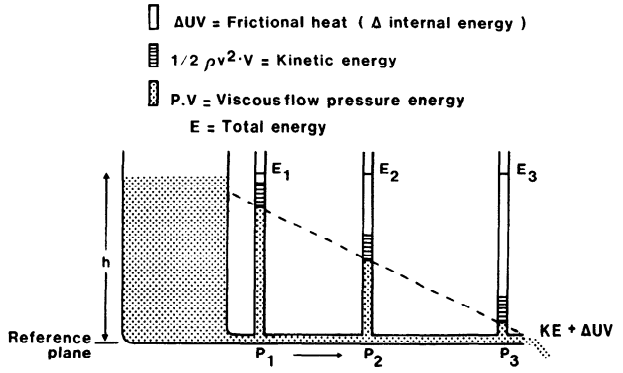


Figure 2

Liquid in a reservoir is allowed to *fall* from a higher level of total energy to a lower level after passing through a rigid circular tube of uniform diameter placed horizontally (open system). Lateral pressures along the tube are recorded by vertical side tubes. Note various components of energy at points 1, 2, and 3, particularly the gradient of *viscous flow pressure.* Other things being equal, the flow rate and velocity (hence kinetic energy) and viscous flow pressure gradient vary with *h.* Similarly, the gradient will vary with total resistance to flow (length and diameter of tube and viscosity of liquid). This model may give the false impression that in the circulatory system gravitational energy of blood plays a similar role in driving the blood. This does not occur because the circulatory system is not an "open system."

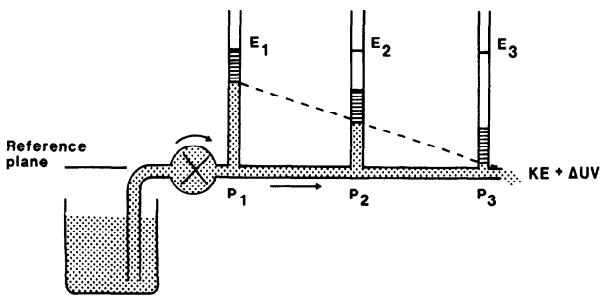


Figure 3

A pump is used to induce a *steady* nonturbulent flow in a circular rigid tube of uniform diameter placed horizontally. Height of the liquid in vertical side tubes at points P_1, P_2, and P_3 registers *viscous flow* pressures along the tube. Pressure *drop* (gradient) between two points ($P_1 - P_2$, $P_2 - P_3$) is the perfusion or driving pressure and is an expression of energy "loss" in the form of frictional heat. In such a horizontal tube of uniform diameter, gravitational pressure energy, gravitational positional energy, and kinetic energy of the liquid are the same at all points along the tube. Hence they play no role in driving the liquid. *Viscous flow* pressure gradient ($P_1 - P_3$) varies with flow rate ($\dot{Q}$) and total resistance (R) between the two points in accordance with Poiseuille's equation ($P_1 - P_3 = \dot{Q} \cdot R$). Resistance in such a single tube varies with distance between P_1 and P_3, diameter of the tube, and viscosity of the liquid.

liquid along the length of the tube, in accordance with the modified Bernoulli's equation, are shown in the vertical side tubes (piezometer tubes). The lateral (or transmural) pressure, which is related to the flow of the liquid against the viscous resistance of the tube, is the *flow pressure* because the liquid is in motion. It represents the conversion of gravitational potential energy of the liquid at the top to flow pressure through the conduit. A smaller conversion is to kinetic energy. Since the tube is of uniform diameter, the linear velocity of flow and the kinetic energy at different points along the tube remain constant ($v = \dot{Q}/A$). The loss of viscous flow pressure energy along the tube is in the form of frictional heat (ΔUV). It varies with flow rate ($\dot{Q}$) and the total resistance (R) to flow. $\dot{Q}$ varies with the height (h) of the liquid in the reservoir and with R, which varies with the distance between the points, the diameter of the tube, and the viscosity of the liquid (Poiseuille's equation, $P_1 - P_2 = \dot{Q}\, 8L\eta/\pi r^4$, where L is the length of the tube, η is the coefficient of viscosity, and r is the radius of the tube). The liquid that runs to a lower level of gravitational potential energy also carries away the kinetic energy (developed by converting the positional energy of the liquid at the top) and part of the frictional heat that has developed in the liquid (some heat may be lost to the tube).

It is unfortunate that models in which gravity causes flow have been used extensively to illustrate the Poiseuille equation. Such models tend to give the *false impression* to the biologist that gravity plays a similar role in driving or opposing blood flow in the circulatory system. Nothing can be further from the truth.

To avoid such false impressions, it is preferable to *use a pump* instead of gravity to drive liquid in a rigid tube of uniform diameter placed horizontally. This position will prevent gravity from inducing flow. Figure 3 shows the energy components in a pump-driven liquid that flows streamline at uniform velocity in a horizontal rigid tube. The flow pressure gradient (*perfusion* or *driving pressure*) obeys the Poiseuille equation.

The next model is a circuit in which liquid is driven steadily by a pump in a *rigid system* of tubes of uniform diameter that is directed downward and returns the liquid up to the reservoir (Figure 4). In other words, the liquid does not "fall" to a lower level of energy by gravity but is returned to its *original gravitational position.* This arrangement has an unexpected and remarkable effect on the dynamics of flow. *Understanding the dynamics of this design is crucial for a proper concept about the effect of gravity on circulatory dynamics.*

In this circuit (Figure 4), the pressure at any point is the sum of flow pressure and gravitational pressure. However, the added gravitational pressure at P_2 and P_3 (ϱgh) neither facilitates nor hinders flow because of the operation of the siphon principle. It is often believed,

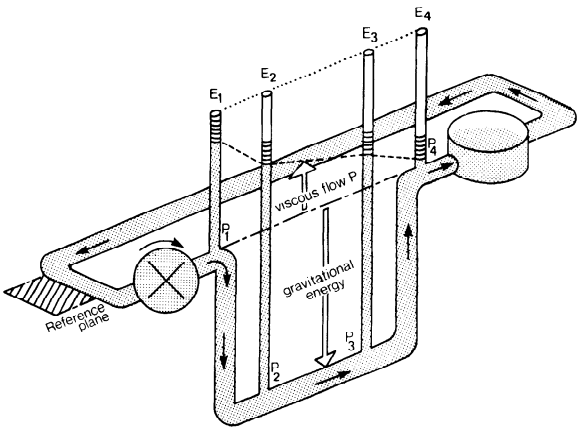


Figure 4

Pump-driven streamline flow in a circuit that returns the liquid to the reservoir through a system of rigid tubes of uniform diameter placed vertically. Viscous flow pressure gradient is indicated by the *dashed lines.* Note that the pressure at any point is equal to *viscous flow* pressure + gravitational pressure (ϱgh) measured from the reference plane. In such a circuit where the liquid is returned to its original level, gravitational pressure and position energies in the upward limb are balanced by gravitational pressure and position energies in the downward limb (siphon principle). Thus gravity neither facilitates downward flow nor hinders upward flow. Energy driving the liquid is the pressure gradient developed by the pump against viscous resistance of the circuit.

erroneously, that the pump must spend extra energy to overcome the gravitational pressure in the upward limb of the circuit. This is far from being the case because the *gravitational pressure and positional energy of the liquid in the upward limb is exactly counterbalanced by the gravitational pressure and positional energy of the liquid in the downward limb.* This feature is essentially the siphon principle. If this counterbalancing characteristic is overlooked, erroneous concepts will prevail, as is often the case. In this model, the kinetic energy does not contribute to flow because it is the same throughout the system on account of uniform diameter and velocity. The only driving force that operates is the flow pressure gradient developed by the pump against the viscous resistance of the circuit. This gradient is indicated by the uniform drop of pressure (dashed lines in Figure 4).

The important concept derived from this *U-shaped tube system* model is that *although* gravitational energy of the liquid *potentially* facilitates downward flow and potentially hinders upward flow, these two opposing actions counterbalance each other as the liquid is returned to its *original level,* resulting in a null effect. The pump has to overcome only the viscous resistance of the circuit.

If this circuit were oriented horizontally or *upward instead of downward,* the pump would consume exactly the same amount of energy.

To illustrate further the effect of upward flow, consider the model in Figure 5. When the pump drives the liquid to a *higher gravitational positional energy* through a rigid tube (Figure 5, *path a*), the pump must overcome not only the viscous resistance of the tube system ($\dot{Q} \cdot R$) but also the gravitational pressure of the vertical column of liquid up to the aperture (ϱgh). In this case the pump does work to move the liquid to a higher energy level. On the other hand, if the same tube is bent to an inverted U so that the liquid is returned to the *original level of gravitational potential energy* (Figure 5, *path b*), the pump uses less energy because the gravitational energy of the liquid in the upward limb is counterbalanced by the gravitational energy in the downward limb (siphon effect). The pump now has to drive only against the viscous resistance of the system ($\dot{Q} \cdot R$). It is remarkable that such a minor change in design has such an important effect on the dynamics of flow.

At this point a word of caution is necessary. The circulatory system is not a rigid system as in these models but is distensible (or collapsible), which has important effects on vascular capacitance and resistance to flow.

Let us now apply these principles in a general way to the circulatory system, neglecting the pulsatile nature of flow, curvature of vessels, bifurcation effects, and so forth. First of all, the circulatory system is a closed and supporting system so that gravity cannot cause the flow of blood to a lower level of energy (proved by the fact that arrest of the heart stops the flow). The pumping activity of the heart creates pressure gradients in the vascular system and induces flow *against the viscous resistance of the circuit* and returns the blood to the *level of the pump.* In the horizontal position of the body, it is this flow pressure gradient that essentially prevails and drives the blood to sustain life. Gravitational pressures of blood are negligible due to short dorsoventral distances. In the aorta the mean viscous flow pressure in a resting individual is about 100 mmHg, which drops to about 2 mmHg in the right atrium. In other words, practically all the flow pressure energy imparted to the blood by the left ventricle is dissipated as heat.

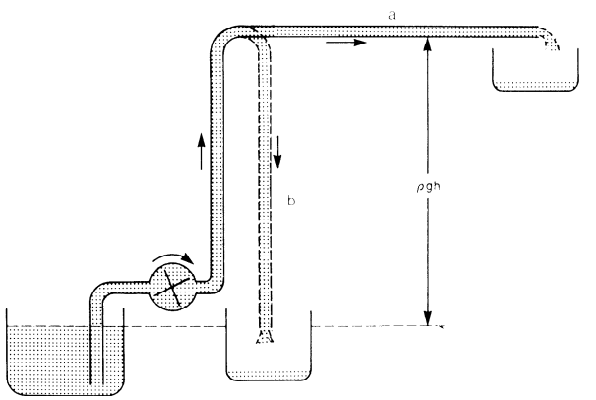


Figure 5

Path a: pump consumed energy not only against the viscous resistance of the tube system to flow ($\dot{Q} \cdot R$) but also against gravitational pressure of the liquid column extending from surface of the liquid in the reservoir to aperture of the outlet (ϱgh). Work is done to lift the liquid to a higher gravitational energy level. *Path b:* if the horizontal tube is inverted as shown, the pump works only against viscous resistance to flow. Facilitatory effect of gravity on the descending limb balances the opposing effect of gravity on the ascending limb (siphon effect). In this arrangement, there is no change in gravitational potential energy of the liquid.

On standing upright, the long columns of blood in the systemic circuit are subjected to the action of gravity. In this position, *gravitational* pressure (ϱgh) of blood is added to the *viscous flow* pressure gradient developed by the left ventricle. Since the right atrial pressure remains practically zero under all positions of the body, it is taken as the reference level. On standing upright, the vascular pressures (both arterial and venous) above the level of the right atrium fall by the height of blood columns (ϱgh) and increase in all the vessels below the heart. These added pressures do not hinder upward flow or facilitate downward flow of blood as explained in the models of Figures 4 and 5 (siphon principle). Stated in another way, the heart does not overcome the added gravitational pressure of blood to drive uphill in arteries above the heart or to drive uphill in veins below the heart.

On the other hand, upright posture has marked *secondary* effects on circulation. These are brought about by changes in the total lateral (transmural) pressure in vessels. The increase in vascular pressure below the level of the heart distends all vessels, particularly the veins, causing pooling of blood and thus decreases the venous return to the heart from these regions.

At the same time, the drop in vascular pressure above the heart causes partial collapse of the veins, thereby increasing their resistance to flow. More importantly, the drop in carotid sinus pressure causes reflex peripheral vasoconstriction in the skin, subcutaneous tissues, skeletal muscles, and the abdominal organs.

The lung vessels (being highly distensible) are also subjected to gravitational effects resulting in collapse of apical and distension of the basal vessels, thereby decreasing the blood flow to the lung apices and increasing the flow to the lung bases.

The overall effect of all these is to decrease the venous input to the heart and cardiac output, which may be reduced by as much as 20%.

It is worth noting that in the astronaut who is orbiting in a space capsule the gravitational pressure gradients of blood are eliminated and positional changes of the astronaut have no effect on circulation.

With regard to the kinetic energy term ($\frac{1}{2}mv^2$), it must be emphasized that this energy can be converted to viscous flow pressure energy and vice versa. Herein lies many practical applications of Bernoulli's equation, often described as Bernoulli's principle. This principle states that *when velocity of flow incrases* [which implies increased kinetic energy ($\frac{1}{2}mv^2$)], *there is a proportional drop in pressure energy* and *vice versa.* Thus the two energies are interconvertible (Figure 6). Practical uses of this principle are numerous, e.g., atomizers, garden sprays of chemicals, paint sprays, aspirators, flow-measuring devices like Venturi meters, suction of fuel in carburetors. An interesting observation may be made in a shower having a curtain; increasing the velocity of water flow pulls the shower curtain inward due to the drop in air pressure.

An illustration of the Bernoulli equation in the circulatory system (though not strictly applicable to pulsatile flow) is the flow from the left ventricle to the aorta during the latter part of ventricular ejection. During this period there is a reversal of the pressure gradient (3, 5) in which part of the kinetic energy (or momentum) of ventricular blood is converted into pressure energy of the blood in the aorta. One possible factor is that as the blood is ejected, the aorta distends (stores potential energy), increasing its cross-sectional area and thereby reducing the velocity and kinetic energy of the aortic blood. Thus part of the kinetic energy of ejected ventricular blood is converted into pressure energy in the aorta. This simplistic concept overlooks inertia effects of pulsatile flow from the ventricle and other complex factors such as turbulence in aortic flow.

The importance of kinetic energy must be remembered when arterial pressure is recorded with a catheter. The direction of the opening of the tip will influence the pressure reading. If the opening is opposite to the direction of flow, the pressure recorded is higher than lateral pressure because the kinetic energy of the moving liquid that is arrested at the opening is converted into pressure

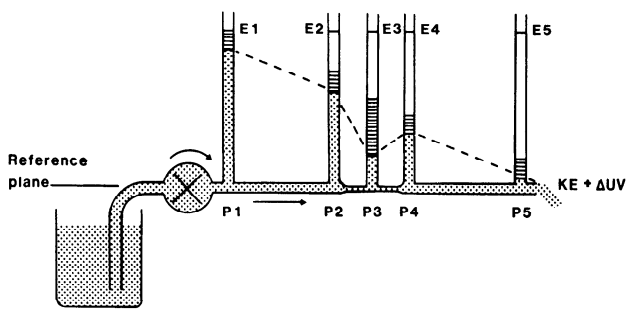


Figure 6
Liquid is driven through a rigid tube that has a constricted section along its length. In the narrow region velocity increases because flow is the same, but cross-sectional area is reduced. Increased velocity increases kinetic energy ($\frac{1}{2}mv^2$) that occurs at the expense of viscous flow pressure energy (Bernoulli principle). In the wider area after the constriction (P_4) some of the kinetic energy is reconverted into pressure. Hence flow can occur from a low pressure in constricted region to a higher pressure down the stream because flow is due to gradients of total energy. Total energy (including thermal) remains practically constant (law of conservation of energy), assuming no heat is transferred to the tube and its surroundings.

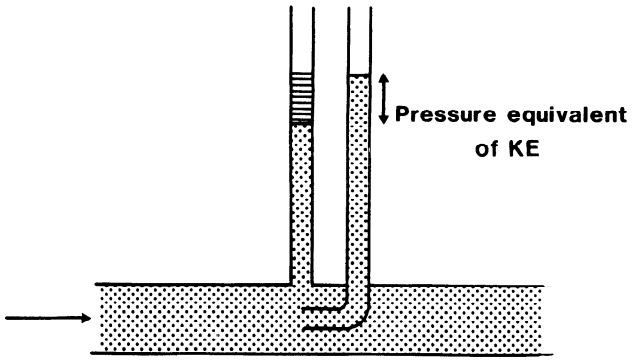


Figure 7
Influence of direction of aperture of recording probe on the pressure recorded. When the opening of the probe "faces" the flow, kinetic energy of the arrested liquid is converted into pressure energy and the reading is greater than the lateral pressure by an amount equal to $\frac{1}{2}mv^2$ (diagram assumes that velocity front is square).

(Figure 7).[2] If the opening is directed downstream, the pressure recorded will be lower than lateral pressure.

Burton (2) has attempted to quantify these energy conversions in the circulatory system. According to him, in a resting person, the kinetic energy of blood at the orifice of the aorta *during ejection* is equivalent to a pressure of about 4 mmHg (neglecting the energy of turbulence that is likely to occur during this period). However, during muscular exercise, with increase in cardiac output and aortic velocity, the kinetic energy of blood in the aorta tends to become significantly greater. Burton also points out that kinetic energy gradients play a more significant role in atrioventricular filling and in the pulmonary circulation, since the dynamic pressures are low and the kinetic energy of blood constitutes a larger fraction of total energy compared with that in the systemic circuit.

At this point we must emphasize that in the Poiseuille equation, $P_1 - P_2$ refers to the viscous flow-pressure gradient only, *excluding the gravitational pressure difference* between the two points (see Figure 4). To illustrate this in the circulatory system let us consider the mean aortic pressure in an upright individual to be about 100 mmHg. In this position, the total lateral pressure exerted against the wall of the dorsalis pedis artery would be about 180 mmHg in a person of average height. This pressure is the sum of about 95 mmHg flow pressure due to viscous resistance and about 85 mmHg pressure due to gravity acting on the column of blood extending from the dorsalis pedis to the aorta ($= \varrho gh$). One may wonder how the blood flows from a pressure of 100 mmHg in the aorta (P_1) to a much higher pressure in the dorsalis pedis artery of about 180 mmHg (P_2). As explained earlier, one must exclude gravitational pressure of blood in the dorsalis pedis because this pressure does not contribute to the driving force of blood in the closed circulatory system. Thus the pressure to consider is the flow pressure, which is 95 mmHg (180 − 85 mmHg). Hence, $P_1 - P_2$ or the perfusion pressure driving the blood from the aorta to the dorsalis pedis is 100 − 95 mmHg = 5

[2]Physicists sometimes refer to the term $\frac{1}{2}\varrho v^2$ of the Bernoulli equation as the "dynamic pressure" (1, 4). This terminology seems to be derived from the fact that arrest of moving fluid (stagnation) converts its kinetic energy into pressure energy as shown in Figure 7. To confuse the terminology further, they refer to the lateral pressure of *moving fluids* as "static pressure" (6). These terms are confusing and inappropriate and their use is not recommended in hemodynamics.

mmHg. This low gradient is an expression of the low resistance of the large arteries.

By the same token, the driving pressure of blood from a vein on the dorsum of the foot is not the total pressure in the vein (90 mmHg) minus right atrial pressure (2 mmHg) but is total pressure (90 mmHg) minus gravitational pressure (85 mmHg) equals flow pressure in vein (5 mmHg) minus right atrial (2 mmHg) equals 3 mmHg.

A similar elimination of gravitational pressure must be made in all other parts of the circulatory system to arrive at the perfusion pressure between any two points. In other words, gravity neither hinders nor facilitates blood flow in the circulatory system by changing the driving pressure. It can and does change flow by altering *vascular resistance* and capacitance (passively and reflexly).

I wish to emphasize again that strictly speaking the modified Bernoulli equation applies only to *steady streamline* flow of liquids. When flow is pulsatile and/or turbulent, the dynamics becomes much more complex and is beyond the scope of this paper.

Summary

Misconceptions on vascular hemodynamics are still prevalent among physiologists and physicians, particularly regarding the effect of gravity. A useful formulation is that of Bernoulli, provided it is modified to include Poiseuille's relationship. The original Bernoulli equation applies to nonviscous (frictionless) liquids flowing streamline. For real liquids the equation must be modified to *include viscous resistance to flow* and internal energy of the liquid. Under such conditions the total energy, including thermal, remains constant at all points along the system. The possible components of total energy are *1*) pressure energy related to viscous flow resistance and to gravity, *2*) gravitational potential or positional energy, *3*) kinetic energy, and *4*) thermal energy. The first three are interconvertible.

In a circuit with a vertical orientation, there are two types of pressure: *1*) pressure related to viscous resistance to flow, described as *viscous flow pressure,* and *2*) pressure due to gravity, described as *gravitational pressure.* If a liquid in a gravitational field, circulated by a pump, returns to its *original gravitational level,* gravity neither hinders upward flow nor facilitates downward flow because gravity acts equally on the outflow and inflow limbs of the circuit counterbalancing each other (similar to the siphon principle). Under these conditions, modified Bernoulli's equation is reduced to three variables: *1*) viscous flow pressure energy developed by the pump, *2*) kinetic energy, and *3*) thermal energy. Flow is dependent on *gradients of viscous flow pressure energy plus kinetic energy* (excluding gravitational pressure and positional energies).

These concepts apply to the circulatory system, except that blood vessels, being distensible, undergo changes in diameter and resistance to flow. Blood flow changes with posture are related to alterations in vascular capacitance and resistance and *not to changes in driving pressure.* $P_1 - P_2$ of the Poiseuille equation refers to *gradients of viscous flow pressure only* (excluding gravitational).

The kinetic energy of blood is negligible in the systemic arteries under resting conditions but may become significant during exercise. It is a relatively larger fraction of total driving energy in the pulmonary circulation and in atrioventricular filling but is often overlooked.

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CME Category I Credits

With this issue *The Physiologist* begins 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 will be 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.

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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.

Functions of the Renal Nerves

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Of the many regulatory systems capable of influencing renal function, the renal nerves have received relatively little attention in the past but have recently been subjected to more rigorous and critical examination. The reasons for this relate to newer observations concerning the functional neuroanatomy of the kidney as well as a broadened appreciation of the fact that high intensities of renal nerve stimulation produce alterations in several aspects of renal function, some of which can independently influence the particular variable under scrutiny, thus rendering a clear and precise interpretation impossible.

Renal Neuroanatomy

Relative to its size, the kidney has a richer innervation than almost any other organ. Electron-microscopic and histochemical fluorescence methods have been used to demonstrate a predominantly noradrenergic innervation of the afferent and efferent arterioles, the juxtaglomerular apparatus, the proximal and distal convoluted tubules, and the thick ascending limb of the loop of Henle. Dopamine-containing neuronal elements have been found at the glomerular vascular pole. Both histochemical and functional observations exclude a role for renal cholinergic innervation. Efferent unmyelinated fibers predominate over afferent myelinated fibers. Direct or reflex-induced increases in efferent renal sympathetic nerve activity increase the release of norepinephrine and dopamine but not epinephrine into renal venous blood and urine. The kidney is able to synthesize dopamine from circulating dopa in nonneuronal tissue. Radioligand binding studies indicate that both glomeruli and tubules poşsess α- and β-adrenoceptors as well as dopamine receptors.

Effects on Renal Vasculature

Activation of the efferent renal nerves produces renal vasoconstriction; there is no functional evidence to support the existence of sympathetic cholinergic vasodilator fibers in the kidney. Direct electrical stimulation of the efferent renal nerves produces frequency-dependent decreases in renal blood flow and glomerular filtration rate, which are abolished by renal α-adrenoceptor (α_1) or ganglionic blockade. However, renal blood flow is not affected by the ~60% increase in efferent renal nerve activity produced by carotid sinus baroreflex activation. Similarly, withdrawal of basal efferent renal nerve activity by renal denervation does not affect renal blood flow. Thus, although pulse synchronous efferent renal nerve activity is easily demonstrated, its importance for the control of renal hemodynamics under normal physiological circumstances is unclear. However, much greater increases in efferent renal nerve activity, ~500%, as elicited by environmental auditory stimuli, produce profound renal vasoconstriction. The response of the renal vasculature to alterations in efferent renal nerve activity is influenced by its capacity to autoregulate renal blood flow over a wide range of renal perfusion pressures.

Phenoxybenzamine administration increases the renal venous outflow of norepinephrine during renal nerve stimulation. This constitutes phenomenological evidence for the existence of presynaptic α-adrenoceptors (α_2) in the kidney, which mediate an inhibitory effect on the release of norepinephrine from the nerve terminal. However, no evidence has been forthcoming to demonstrate a functional role for these receptors in the control of the renal circulation.

Recent direct microvascular studies show that norepinephrine produces greater reductions in the luminal diameter of the afferent than the efferent glomerular arteriole, whereas angiotensin II produces greater reductions in the luminal diameter of the efferent than the afferent glomerular arteriole. These differential effects explain the alterations in renal blood flow and glomerular filtration rate following renal nerve stimulation. Renal nerve stimulation that reduces renal blood flow by 15% does not decrease glomerular filtration rate except in the presence of angiotensin II receptor antagonists or converting enzyme inhibitors. Renal nerve stimulation releases norepinephrine, which preferentially constricts the afferent glomerular arterioles, decreasing renal blood flow, whereas the angiotensin II release preferentially constricts the efferent glomerular arterioles to maintain glomerular hydrostatic pressure and, thus, glomerular filtration rate constant. In the presence of angiotensin II receptor antagonists or converting enzyme inhibitors, the compensatory constriction of the efferent glomerular arteriole is prevented, allowing glomerular hydrostatic pressure and glomerular filtration rate to decrease.

Another humoral system that is involved in the neurohumoral control of renal hemodynamics is the prostaglandins. During dietary sodium restriction, as with renal nerve stimulation, there is an increased renal release of norepinephrine, renin, and prostaglandins. Under these experimental conditions as well as in certain clinical conditions characterized by avid renal sodium retention in the presence of reduced effective intravascular volume with heightened neurohumoral renal vasoconstrictor tone (cirrhotic ascites, nephrosis, cardiac failure), administration of prostaglandin synthesis inhibitors decreased renal blood flow, glomerular filtration rate, and urinary water and sodium excretion. Thus

elevated prostaglandin synthesis is an important part of the renal adaptive mechanism to maintain renal blood flow and glomerular filtration rate in the presence of increased neurohumoral renal vasoconstrictor tone in states of reduced effective intravascular volume.

Effects on Renal Tubules

For the renal nerves to participate in the control of renal tubular electrolyte and water transport, it was reasonable to believe that increases or decreases in efferent renal nerve activity would produce reciprocal changes in renal electrolyte and water excretion. To decrease efferent renal nerve activity, renal denervation was used; to increase efferent renal nerve activity, direct or reflex renal nerve stimulation techniques were used. The results of such studies were difficult to interpret in view of several confounding variables. Anesthetic and surgical stress both increase basal efferent renal nerve activity so that any response to renal denervation was deemed an artifact of the preparation. Rigorous physiological evidence verifying the completeness of renal denervation was seldom provided. Direct or reflex renal nerve stimulation intensities were generally large, thus altering renal blood flow and glomerular filtration rate, which obscured the identification of direct renal tubular effects. Recently, several findings in both experimental animals and humans clearly indicate that the efferent renal sympathetic nerves can directly influence the renal tubular transport of sodium and water independent of changes in renal blood flow, glomerular filtration rate, or circulating humoral agents. Studies have been conducted in conscious unanesthetized animals that unequivocally demonstrate a role of the renal innervation in the regulation of renal tubular sodium and water transport. The denervated kidney of conscious rats exhibits an increase in urinary water and sodium excretion unaccounted for by changes in glomerular filtration rate or renal blood flow during both euvolemic and volume-expanded conditions. Furthermore, in both conscious rats and dogs, renal denervation impairs the renal adaptive response to dietary sodium restriction, resulting in abnormal renal sodium loss and negative sodium balance. In these several studies, verification of the completeness of renal denervation has been performed using several techniques: abolition of the renal vasoconstrictor response to electrical stimulation of the proximal renal nerve bundle, disappearance of renal tissue catecholamine content measured either biochemically or by tissue histofluorescence techniques. In addition, several studies have demonstrated that low-frequency renal nerve stimulation ($\sim$1.0 Hz) decreases urinary sodium and water excretion without changing glomerular filtration rate, renal blood flow, or its intrarenal distribution. This increase in renal tubular sodium and water reabsorption is not mediated by either prostaglandins or angiotensin II and, using renal micropuncture techniques, has been localized to both the proximal convoluted tubule and the loop of Henle. Additional studies employing specific adrenoceptor antagonists indicate that this neurally regulated increase in renal tubular sodium and water reabsorption is mediated via α_1-adrenoceptors; neither α_1- nor β-adrenoceptors are involved.

Studies in conscious rats and dogs subjected to environmental stress have demonstrated an integrated cardiovascular and renal response, the latter consisting of an antidiuresis and antinatriuresis without changes in glomerular filtration rate or renal blood flow. The excretory responses are abolished by renal denervation or by intravenous administration of those β-adrenoceptor blocking agents that tend to more readily cross the blood-brain barrier and accumulate in the brain (e.g., propranolol). The observations suggest that environmental stress activates a mechanism mediated by β-adrenoceptors located in the central nervous system which produces an increase in efferent renal sympathetic nerve activity leading to the antidiuresis and antinatriuresis.

Further evidence in support of this concept derives from studies involving physiological reflex decreases in efferent renal sympathetic nerve activity. Stimulation of left atrial mechanoreceptors (increased left atrial pressure) with vagal afferents as by left atrial balloon inflation or reversible mitral stenosis decreases efferent renal sympathetic nerve activity and plasma antidiuretic hormone concentration; the result is a diuresis and natriuresis without changes in glomerular filtration rate, renal blood flow, or its intrarenal distribution. The diuresis is dependent on the decrease in plasma antidiuretic hormone concentration, since it does not occur in hypophysectomized dogs given constant infusions of antidiuretic hormone. The natriuresis is dependent on the decrease in efferent renal sympathetic nerve activity, since it does not occur if the kidneys are denervated. The diuresis, natriuresis, and decrease in efferent renal sympathetic nerve activity are abolished by prior vagotomy. These findings support the existence of a neural mechanism for the regulation of extracellular fluid volume which resembles a classic neural reflex arc (Figure 1). There is an afferent limb consisting of a sensor, which continually monitors the extracellular fluid volume, and an afferent neural pathway that conveys information from the sensor to an integrative site in the central nervous system. From this integrative site there is an efferent limb consisting of neurohumoral pathways that influence the function of effector organs, which ultimately produce the appropriate changes in the extracellular fluid volume. The left atrial mechanoreceptor fulfills the requirements for a sensor in the low-pressure vascular system: it possesses a well-defined compliance relating intravascular volume to filling pressure and responds to changes in wall tension (stretch) by discharging into afferent vagal fibers with central nervous system

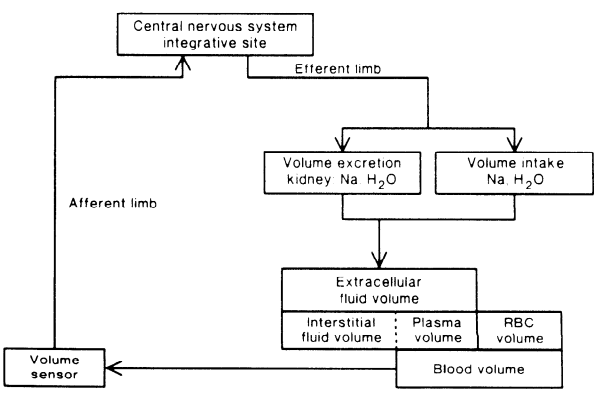

Figure 1
Pathways for the regulation of extracellular fluid and plasma volume by a reflex mechanism involving the autonomic nervous system.

projections in both the medulla oblongata and the supraoptic and paraventricular nuclei of the hypothalamus. The efferent neurohumoral pathways participate in an integrated response consisting of alterations in plasma antidiuretic hormone concentration, efferent peripheral sympathetic neural outflow to the pre- and postcapillary peripheral resistance vessels, and efferent renal sympathetic nerve activity. These signals to the effector organs produce changes in thirst and water intake, renal water and sodium excretion, and fluid movement between the blood volume and the interstitial fluid volume compartment.

The importance of the renal nerves in the regulation of external sodium balance in humans is supported by the fact that production of autonomic blockade by guanethidine administration to normal subjects resulted in an impairment of the normal renal adaptive response to dietary sodium restriction. Similarly, patients with the syndrome of idiopathic autonomic insufficiency (Shy-Drager syndrome) cannot sufficiently reduce urinary sodium excretion so as to achieve external sodium balance in the face of dietary sodium restriction. The efferent renal sympathetic nerves may constitute an important mechanism for the enhanced renal tubular sodium and water reabsorption characteristic of edema forming states. In experimental congestive heart failure, a natriuretic response is observed following pharmacological renal denervation. In human subjects with cirrhotic ascites, a natriuretic response is observed following immersion to the neck of euthermal water, a maneuver which is known to increase central blood volume and left atrial pressure and stimulate cardiopulmonary mechanoreceptors. The natriuretic response is accompanied by significant decreases in the circulating plasma concentrations of renin, aldosterone, antidiuretic hormone, and norepinephrine but not epinephrine; the increase in urinary sodium excretion showed a strong negative correlation with the decrease in plasma norepinephrine concentration. Although peripheral plasma norepinephrine concentration may not be a precise index of increased regional sympathetic outflow, it is known that there is a positive renal venoarterial difference for plasma norepinephrine concentration in human subjects with cirrhotic ascites. Since the renal venoarterial difference for plasma norepinephrine concentration is negative in the denervated kidney and becomes increasingly positive at higher frequencies of renal nerve stimulation, these several observations suggest the existence of an increase in efferent renal sympathetic nerve activity that contributes to the avid renal tubular sodium reabsorption characteristic of human subjects with cirrhotic ascites.

Thus these several observations in both humans and experimental animals indicate that the efferent renal sympathetic nerves represent an important mechanism for the direct regulation of renal tubular sodium and water reabsorption in both physiological and pathophysiological conditions.

Effects on Renin Secretion

Three major mechanisms are involved in the secretion of renin by the juxtaglomerular granular cells: the renal vascular baroreceptor, the tubular macula densa receptor, and renal sympathetic tone (humoral or neural). To assess the role of a single mechanism in the control of renin secretion, it is essential to eliminate or regulate the influence of other mechanisms known to affect renin secretion. Although high-intensity renal nerve stimulation increases renin secretion, it is difficult to isolate and identify the influence of efferent renal sympathetic nerve activity per se because of the resultant alterations in input stimuli to the other mechanisms for renin secretion, i.e., changes in renal blood flow and renal vascular resistance (baroreceptor mechanism) and changes in the composition, delivery, or transport of sodium chloride-containing fluid at the macula densa (macula densa receptor mechanism). Recently, however, several intensities of renal nerve stimulation have been identified that have permitted a more precise analysis of the contribution of each mechanism to the increase in renin secretion produced by activation of the efferent renal sympathetic nerves. Initially, renal nerve stimulation at frequencies ≤ 1 Hz decreased urinary sodium excretion and increased renin secretion without affecting renal perfusion pressure, renal blood flow, or glomerular filtration rate. However, it remained possible that the decrease in urinary sodium excretion might have contributed to the increase in renin secretion via activation of the macula densa receptor mechanism. Subsequent studies have demonstrated that renal nerve stimulation at a frequency of 0.5 Hz increases renin secretion without affecting renal arterial pressure, renal blood flow, glomerular filtration rate, urinary flow rate, or sodium excretion. Thus, in the absence of alterations in input stimuli to the other known mechanisms for the regulation of renin secretion, renal nerve stimulation at 0.5 Hz can be viewed as an isolated neural stimulus to the juxtaglomerular granular cells for renin secretion. The resultant renin secretion is mediated by β_1-adrenoceptors, and no involvement, either stimulatory or inhibitory, of α-adrenoceptors is observed. This level of renal nerve stimulation also increases renal prostaglandin E_2 secretion, which contributes to the increase in renin secretion, since the latter is partially attenuated by administration of either of the prostaglandin synthesis inhibitors, indomethacin or meclofenamate.

At higher intensities of renal nerve stimulation, at frequencies that produce marked renal vasoconstriction (2–3 Hz), a more complex analysis is required because of activation of the other mechanisms involved in the control of renin secretion. The renin secretion response is partially inhibited by β_1-adrenoceptor antagonists (direct neural stimulation of juxtaglomerular granular cells) and partially inhibited by α-adrenoceptor antagonists (baroreceptor and macula densa receptor mechanism); the combination of β_1- and α-adrenoceptor antagonism completely inhibits the renin secretion response. Prostaglandin synthesis inhibition also partially inhibits the renin secretion response, but it does not increase the degree of inhibition over that achieved with α-adrenoceptor antagonism alone; these results suggest that the prostaglandin involvement is secondary to (in series with) the α-adrenoceptor-mediated renal vasoconstriction.

An interaction between the neural and nonneural mechanisms for renin secretion is observed at very low intensities of renal nerve stimulation (0.25 Hz), which produce no changes in renin secretion, renal hemodynamics, or excretory function. When renal arterial pressure is reduced below the level of autoregulation of renal blood flow and glomerular filtration rate, renin secretion is markedly augmented by the application of

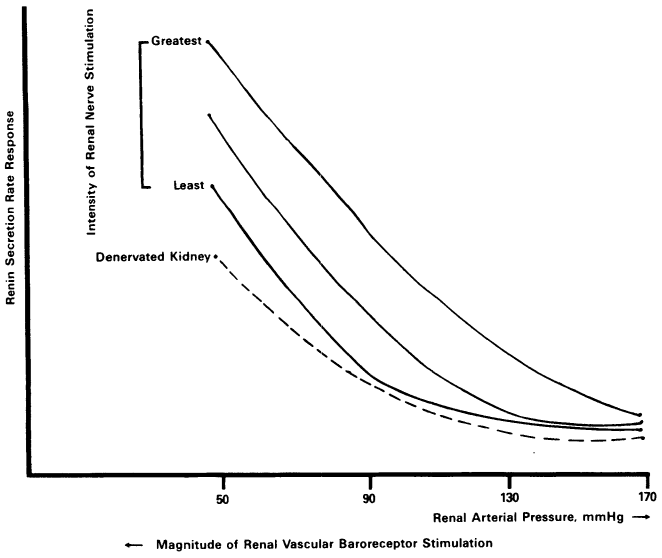

Figure 2
Interactions between neural mechanism (intensity of renal nerve stimulation) and renal vascular baroreceptor mechanism (renal arterial pressure) for renin secretion.

renal nerve stimulation at 0.25 Hz. This augmentation of renin secretion is not observed in the absence of a functioning macula densa receptor mechanism (nonfiltering kidney preparations) nor when the reduction in renal arterial pressure is restricted to the lower limit of autoregulation of renal blood flow and glomerular filtration rate. However, slightly higher levels of efferent renal sympathetic nerve activity, such as those prevailing in the innervated kidney, do augment the renin secretion response to reductions in renal arterial pressure over the entire range when compared with the renin secretion response of the denervated kidney. This neural augmentation is mediated by β_1-adrenoceptors located on juxtaglomerular granular cells. Thus (Figure 2), when renal arterial pressure is low and the renal vascular baroreceptor is strongly stimulated, low intensities of renal nerve stimulation are sufficient to produce an augmented renin secretion rate response. At higher renal arterial pressures when the renal vascular baroreceptor is less stimulated, greater intensities of renal nerve stimulation are required to produce an augmented renin secretion rate response.

Reflex increases or decreases in efferent renal sympathetic nerve activity influence renin secretion, the result depending on a complex interaction between the inputs from carotid and aortic high-pressure baroreceptors and cardiopulmonary low-pressure baroreceptors and the degree to which the nonneural (vascular baroreceptor and tubular macula densa receptor) mechanisms are engaged.

Renorenal Reflexes

Interventions on one kidney are capable of producing functional responses in the ipsilateral or contralateral kidney that are neurohumorally mediated; these are called renorenal reflexes. Two general classes of renal receptors giving rise to increased afferent and either contralateral and/or ipsilateral efferent renal nerve activity upon specific stimulation have been identified neurophysiologically. Renal mechanoreceptors respond to increases in ureteral or renal venous pressure and mechanical compression of the kidney; a common stimulus of increased intrarenal pressure is suggested. Two types of renal chemoreceptors have been identified: those responding to renal ischemia (R_1) as produced by renal artery occlusion or hypoxia and those responding to changes in the chemical environment of the renal interstitium (R_2) as produced by changes in the excretory function of the kidney and the passage of ions from the renal pelvis across the pelvic epithelium. Providing significance for these neurophysiological descriptions are studies of related renal functional alterations. Renal mechanoreceptor stimulation by increasing ureteral pressure results in ipsilateral renal vasodilation and contralateral renal vasoconstriction. The contralateral renal vasoconstriction, but not the ipsilateral renal vasodilation, is dependent on bilaterally intact (afferent and efferent) renal innervation; in addition, the response is abolished by T_6 spinal cord section, indicating that it is not a local spinal reflex and that higher neural centers are involved. The response to ipsilateral renal denervation is an ipsilateral diuresis and natriuresis and a compensatory contralateral antidiuresis and antinatriuresis; acute or chronic denervation of the contralateral kidney reverses or prevents this compensatory antidiuretic and antinatriuretic response. Comparison of mechanoreceptor (increased ureteral pressure) and R_2-chemoreceptor (pelvic perfusion with hypertonic saline) stimulation in the dog shows that renal mechanoreceptor stimulation elicits a greater contralateral renorenal reflex response (renal hemodynamics, renin secretion) than does renal R_2-chemoreceptor stimulation. Likewise, in the dog, stimulation of renal mechanoreceptors by increasing ureteral pressure or increasing renal vein pressure to the same level of intrarenal (needle) pressure elicits a quantitatively similar contralateral renorenal reflex response. In the rat (Figure 3), both renal mechanoreceptor and R_2-chemoreceptor stimulation elicit a contralateral renorenal reflex response consisting

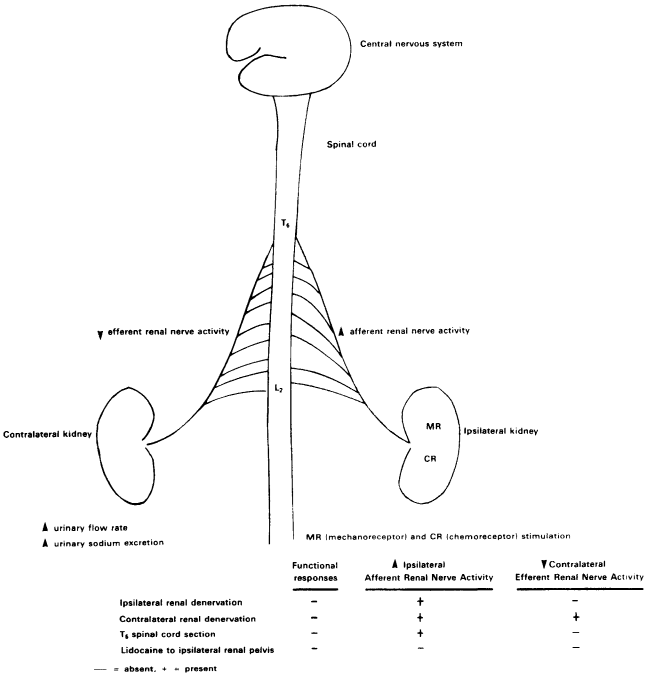

Figure 3
Renorenal reflexes.

of a diuresis and natriuresis without a change in renal blood flow, glomerular filtration rate, or mean arterial pressure. Denervation of either kidney abolishes the contralateral diuretic and natriuretic responses, and neurophysiological recording studies demonstrate a simultaneous increase in ipsilateral afferent renal nerve activity and decrease in contralateral efferent renal nerve activity. Instillation of lidocaine into the ipsilateral renal pelvis abolishes the contralateral diuretic and natriuretic responses as well as the changes in both ipsilateral afferent and contralateral efferent renal nerve activity.

Hypertension

Renal denervation has been shown to delay the onset or lessen the severity of hypertension in a variety of experimental forms of hypertension in animals. Since the effect was not related to changes in renal sodium and water excretion or renin release, attention was turned away from the efferent renal nerves and was focused on the afferent renal nerves. Afferent renal nerve stimulation produces a reflex cardiovascular response consisting of renal and mesenteric vasoconstriction and hindquarters vasodilation. This is a similar response to that obtained with electrical stimulation of the anterior portion of the ventral third cerebral ventricle (AV3V). Evidence that the afferent renal nerves project to the AV3V and the anterior hypothalamus was provided by the demonstration that an acute AV3V lesion abolished the regional vascular resistance changes produced by afferent renal nerve stimulation. In addition, renal denervation produced decreases in hypothalamic norepinephrine concentrations and peripheral sympathetic vascular tone. Stimulation of renal chemoreceptors with renal arterial adenosine infusion increases ipsilateral afferent renal nerve activity, plasma norepinephrine concentration, and arterial pressure. The rise in arterial pressure is reversed by ganglionic blockade and prevented, along with the increase in plasma norepinephrine concentration, by prior renal denervation. These studies support the view that renal receptors with afferent renal nerve fibers projecting to the AV3V region of the hypothalamus can modulate central mechanisms which regulate peripheral sympathetic outflow which, in turn, influence regional vascular resistance and arterial pressure.

Conclusions and Summary

The renal nerves, both afferent and efferent, participate in the direct and reflex regulation of several major renal functions (Table 1). The kidney, having a pivotal role in the maintenance of water and electrolyte balance and producing vasoactive hormones, is an important organ involved in overall volume and cardiovascular regulation and the maintenance of arterial pressure. Thus the neural regulation of renal function, as summarized herein, represents an important control mechanism governing the contributions of the kidney to the maintenance of normal homeostasis and to the development and maintenance of diverse clinicopathophysiological conditions.

Table 1
Renal Functional Effects of Renal Nerve Stimulation

Renal Nerve Stimulation Frequency	Renin Secretion Rate (RSR)	Urinary Sodium Excretion ($U_{Na}V$)	Glomerular Filtration Rate (GFR)	Renal Blood Flow (RBF)
0.25 Hz	No effect on basal Augments RSR mediated by nonneural stimuli: occurs when renal arterial pressure reduced to lower limit for RBF and GFR autoregulation; occurs at macula densa, not prostaglandin mediated, abolished by β_1-adrenoceptor blockade	No effect on basal	No effect on basal	No effect on basal
0.50 Hz	Increased without changing $U_{Na}V$, GFR, or RBF: mediated by renal β_1- but not β_2- or α_1- and α_2-adrenoceptors; prostaglandin contribution	No effect on basal	No effect on basal	No effect on basal
1.00 Hz	Increased with decreased $U_{Na}V$ without changing GFR or RBF: mediated by renal β_1- but not α_1-α_2-adrenoceptors; prostaglandin contribution	Decreases without changing GFR or RBF: mediated by renal tubular α_1-adrenoceptors (proximal tubule, loop of Henle); not mediated by renal β- or α_2-adrenoceptors or prostaglandins	No effect on basal	No effect on basal
2.50 Hz	Increased with decreased $U_{Na}V$, GFR, and RBF: mediated by renal α_1- and β_1-adrenoceptors; mediated by prostaglandins (in series with renal α-adrenoceptors)	Decreased: mediated by renal vascular and tubular α_1-adrenoceptors	Decreased: mediated by renal vascular α_1-adrenoceptors with prostaglandin and angiotensin contribution	Decreased: mediated by renal vascular α_1-adrenoceptors

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Functions of the Renal Nerves Multiple Choice Questions

1. The intrinsic innervation of the kidney is mainly:
- *a.* adrenergic
- *b.* cholinergic
- *c.* noradrenergic
- *d.* dopaminergic

2. The intrinsic renal nerve fibers innervate:
- *a.* afferent arteriole
- *b.* efferent arteriole
- *c.* juxtaglomerular apparatus
- *d.* nephron (proximal tubule, loop of Henle, distal tubule)
- *e.* all of the above

3. The renal vascular response to renal nerve stimulation is inhibited by:
- *a.* phenoxybenzamine
- *b.* phentolamine
- *c.* guanethidine
- *d.* prazosin
- *e.* all of the above

4. Renal nerve stimulation increases the renal release of
- *a.* norepinephrine
- *b.* dopamine
- *c.* epinephrine
- *d.* prostaglandin
- *e.* renin
- *f.* all but *c*

5. Renal nerve stimulation can
- *a.* increase renin release but not affect urinary sodium excretion, glomerular filtration rate or renal blood flow at low intensities
- *b.* increase renin release and decrease urinary sodium excretion but not affect glomerular filtration rate or renal blood flow at modest intensities
- *c.* decrease renin release and increase urinary sodium excretion, glomerular filtration rate and renal blood flow at modest intensities
- *d.* increase renin release and decrease urinary sodium excretion, glomerular filtration rate and renal blood flow at high intensities
- *e.* all of the above except *c*

6. The effect of renal nerve stimulation on renal blood flow and urinary sodium excretion is mediated by:
- *a.* α_2-adrenoceptors
- *b.* α_1-adrenoceptors
- *c.* β_1-adrenoceptors
- *d.* β_2-adrenoceptors

7. The effect of renal nerve stimulation on renin release is mediated by:
- *a.* α_1-adrenoceptors
- *b.* α_2-adrenoceptors
- *c.* β_2-adrenoceptors
- *d.* β_1-adrenoceptors

8. The renal nerves are important in renal adaptation to:
- *a.* increased dietary sodium intake
- *b.* reduced dietary potassium intake
- *c.* increased dietary chloride intake
- *d.* decreased dieary sodium intake

9. Subthreshold intensities of renal nerve stimulation:
- *a.* increase the renal release of prostaglandin
- *b.* increase the renal release of kallikrein
- *c.* augment the renin release response to nonneural stimuli
- *d.* decrease urinary sodium excretion
- *e.* decrease renal blood flow

10. Renorenal reflexes are elicited by:
- *a.* ureteral occlusion
- *b.* renal artery occlusion
- *c.* renal vein occlusion
- *d.* retrograde ureteropelvic hypertonic perfusion
- *e.* all of the above

β-Blockers and the Kidney: Implications for Renal Function and Renin Release

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β-Adrenergic antagonists have become one of the most widely used groups of medications since their introduction in Europe in 1962 and their subsequent marketing in the United States in 1968. Indeed, there are already more than 20 cardiovascular and noncardiovascular indications for these agents. In the field of antihypertensive agents alone, β-blockers accounted for ~40% of all new nondiuretic prescriptions written from January through June 1980. This compares with a level of 15% for the same period in 1978. Certainly, a measure of the importance and popularity of these drugs is the current marketing in the United States of six products by as many different manufacturers.

One of the attractive aspects of β-adrenergic blocking agents is the relative lack of important adverse effects. Thus <10% of patients being treated for hypertension discontinue these medications because of side effects. Recently, however, several studies have raised the possibility that the chronic use of β-blockers may be associated with substantial decrements in renal perfusion [Epstein and Oster (5)]. One commentator has even reached the conclusion that β-blockers should therefore not constitute a major regimen for the long-term therapy of patients with essential hypertension. The mechanism(s) whereby β-adrenergic antagonists might reduce renal function is by no means clear.

The purpose of this article is to review and discuss the currently available data on this important and controversial topic. Not surprisingly, most of the literature deals with the renal response in hypertensive patients.

There are six β-blocking medications available in the United States, and it is possible that oxprenolol, another agent with intrinsic sympathomimetic activity (ISA), will be marketed soon. Table 1 summarizes the data regarding the major distinguishing features of these seven medications as well as for several others. These include ISA, membrane-stabilizing activity, cardioselectivity, and lipid solubility [Frishman (9)].

The membrane-stabilizing activity (MSA) of propranolol and other agents (formerly called quinidine-like action) does not actually obtain with currently utilized dosages. Furthermore, it is not clinically relevant except perhaps in the case of a massive overdose.

Lipid vs. Water Solubility

The clinical importance of high water solubility vs. high lipid solubility is unequivocal. The relatively highly water-soluble agents, atenolol and nadolol, are not appreciably metabolized in the liver (less first-pass metabolism), which accounts for their intrinsically longer duration of action, their narrower dose ranges, their elimination in the urine, and the necessity to reduce their dosage in the presence of advanced renal insufficiency. Finally, although controversial, there is considerable evidence suggesting that the water-soluble medications enter the central nervous system to a lesser degree and as a result cause less insomnia, nightmares, and depression.

Table 1
Differential Features of Beta-Adrenoreceptor Antagonists

Agent	Cardioselectivity	Intrinsic-sympathomimetic activity	Membrane-stabilizing activity	High water solubility
		Agents Currently Available in the US for the Treatment of Hypertension		
Propranolol (Inderal)	0	0	+	0
Metoprolol (Lopressor)	+	0	0	0
Nadolol (Corgard)	0	0	0	+
Atenolol (Tenormin)	+	0	0	+
Timolol (Blocadren)	0	0	0	0
Pindolol (Visken)	0	+	0	0
		Additional Agents Available Outside the US		
Acebutolol	+	+	+	0
Alprenolol	0	+	+	0
Tolamolol	+	0	0	?
Penbutolol	0	+	0	0
Oxprenolol	0	+	+	0

Perhaps the two most important pharmacological variables relating to β-blockers are cardioselectivity and ISA. These will now be considered in some detail.

Cardioselectivity

Various tissues and organs contain two distinct types of β-receptors. β_1-Receptors predominate in the heart, kidneys, and adipose tissue. Their stimulation increases heart rate, facilitates electrical conduction, enhances the force of myocardial contraction, and probably augments the release of renin into the renal veins (see below, p. 61), and increases lipolysis. Blockade produces bradycardia, decreased cardiac output, eventual reduction in blood pressure, and inhibition of renin release. In contrast, β_2-receptors predominate in the bronchi, arteriolar smooth muscle, and pancreas. Stimulation of these receptors causes bronchodilation, arteriolar dilation, insulin release, and lactate production. Antagonism is associated with the potential for bronchoconstriction, arteriolar constriction, and decreased insulin release and lactate formation. β_1-blockade generally produces the therapeutic features of adrenoceptor inhibition. Although blockade of the β_2-receptor accounts for many of the undesirable side effects of nonselective β-blockers, the frequency of the other side effects is very much the same for all types of β-blockers.

Cardioselectivity (or β_1-selectivity) refers to the property of such agents as metoprolol and atenolol to inhibit β_1-receptors to a greater extent than β_2-receptors. It should be emphasized that cardioselectivity is a relative rather than an absolute feature (the dose range needed to separate β_1 and β_2 antagonism is quite narrow), and its clinical implications and value remain open to question. Selectivity tends to diminish as the dosage of medication increases into the range necessary for the management of many patients with moderate to severe hypertension. Cardioselectivity does not appear to influence the efficacy of blood pressure lowering. Although, theoretically, stress- or exercise-induced increases in blood pressure might be attenuated by selective as opposed to nonselective agents, with the possible exception of oxprenolol and sotalol, β-blockers appear to have a similar ability to correct hypertension. What selectivity has been suggested to confer is the advantage of a somewhat lesser risk of some of the prominent potential side effects, such as bronchospasm, vasospasm, and interference with carbohydrate metabolism, in the predisposed patient who is considered to require the use of β-adrenoceptor blockade.

Intrinsic Sympathomimetic Activity

Intrinsic sympathomimetic activity or partial agonistic activity (PAA) refers to the property of simultaneously blocking a β-adrenoceptor yet acting to stimulate partially either the same or other β-receptors. Experimentally, this property is identified by slight cardiac stimulation that can be obviated by propranolol. The clinical value of ISA is as yet unestablished and requires further study and elucidation. There are *theoretical* considerations suggesting that ISA may reduce the risk of some of the unwanted physiological consequences of β-blockade. Preliminary clinical evidence raises the possibility that ISA-positive agents tend to limit adverse effects on the heart, the lung, and the peripheral vasculature.

With regard to the heart, ISA-positive agents produce less bradycardia and do not reduce cardiac output in the resting state. Recent studies suggest that exercise tolerance is less impaired, and in the patient with ischemic heart disease the potentially detrimental influence of these drugs on left ventricular function is less.

Renal Hemodynamics in Essential Hypertension

To understand and appreciate the potential significance of the hemodynamic alterations induced by β-blockers and other antihypertensive agents they must be considered in the context of those changes occurring in untreated patients with essential hypertension. The result of a recent, carefully conducted study by Ljungman et al. (14) are instructive. These investigators evaluated renal hemodynamics in 111 untreated, hypertensive male volunteers, all of whom were 49 years of age. Their findings are similar to those previously reported in the literature for comparable subjects. They indicate that with increasing blood pressure there is a progressive decline in renal blood flow and a progressive increase in renal vascular resistance. Since glomerular filtration rate (GFR) did not decrease, there was a progressive increment in filtration fraction. All of these changes occurred gradually from low to high blood pressure and did not start at any particular level. Constancy of GFR in spite of a decrease in renal blood flow implies an increase in the resistance of the efferent arteriole exceeding that of the afferent arteriole. This phenomenon of preservation of GFR, which may be relative, is termed autoregulation of GFR. Teleologically it suggests that, at least in early essential hypertension, renal hemodynamics are altered in such a way as to minimize any decrements in GFR. Obviously, it is important to known which antihypertensive agents tend to exacerbate the renal hemodynamic changes associated with hypertension and/or perturb vs. perpetuate this apparently beneficial autoregulatory phenomenon. In this regard, the recent findings relating to the antihypertensive angiotensin-converting enzyme inhibitor, captopril, are of interest. This medication does not have a detrimental effect on renal hemodynamics in patients with chronic essential hypertension. Recently, however, it has been shown to reduce GFR in patients with bilateral renal artery stenosis, presumably by interfering with angiotensin-dependent compensatory autoregulatory constriction of the efferent arteriole.

Systemic Hemodynamic Effects of Long-Term Therapy of Hypertensive Patients with β-Blockers

The initial administration of a β-adrenoceptor blocker without ISA results in a decline in cardiac output and an increase in total peripheral resistance. These two opposing influences on blood pressure may negate each other. Thus the intravenous administration of a single dose of propranolol generally does not produce a decline in blood pressure. With repeated dosing, cardiac output remains depressed. As peripheral resistance falls toward, but not below, its elevated pretreatment value there is a parallel decrease in blood pressure [Lund-Johansen and Ohm (15)]. The mechanisms for the increase in peripheral resistance remain controversial. They probably relate either to blockade of the arteriolar β_2-receptors, which modulate vasodilation, and/or to a reflex vasoconstriction in response to the decline in cardiac output. Since the increase in peripheral resistance appears to be relatively independent of whether the agent is β_1 selective, the latter mechanism appears to be more important.

The hemodynamic profile characterizing the response to a β-blocker with potent ISA contrasts sharply with the above [Man In't Veld and Schalekamp (16)]. In this case, the cardiac output changes very little during either the initial or longterm phase. The fall in blood pressure is associated with a decline in peripheral resistance *below* the pretreatment level. It is unknown whether the absence of an increase in total peripheral resistance relates to the preservation of cardiac output, to a stimulation of β_2-receptors in the peripheral arterioles, or both. The clinical benefit, if any, of this more favorable alteration of hemodynamics with ISA-positive agents is unknown.

β-Blocker-Induced Changes in Renal Function

In the following sections we will consider the evidence that some β-blockers may induce abnormalities in renal blood flow and glomerular filtration rate.

Changes in Serum Creatinine Concentration and Blood Urea Nitrogen

Except for a few case reports of patients with preexisting renal failure, administration of β-adrenoceptor blockers has not been associated with important elevations of serum creatinine or blood urea nitrogen levels, or else the changes have been relatively trivial. Similarly, in those instances in which GFR and/or renal plasma flow have been measured coterminously, there have been either no changes in these variables or the alterations have been small.

Changes of Renal Hemodynamics Associated with Acute Administration of β-Adrenergic Antagonists

The initial studies of the renal hemodynamic response to the acute administration of β-adrenergic antagonists were carried out in a number of animal models. Several investigators have demonstrated a decrease in renal plasma flow as measured by either flow probe or *p*-aminohippurate clearance following the administration of propranolol. In addition, it was observed that the intravenous administration to dogs of either pindolol or practolol produced slight, statistically insignificant decrements in renal plasma flow and GFR. That this response may not be uniform for all β-blockers was suggested by the study of Duchin et al. (4) who demonstrated a 13% increase in renal plasma flow in dogs in response to nadolol.

There have been relatively few acute studies in humans. Several of the investigations have involved the use of nadolol and the cardioselective medication atenolol, and the medication was generally administered intravenously. In accordance with the findings in experimental animals, the intravenous administration of propranolol by Sullivan et al. (24) resulted in a decrease in renal plasma flow as assessed by ^{133}Xe washout and a concomitant increase in renal vascular resistance. Utilizing standard inulin and *p*-aminohippurate clearance methodology, Schirmeister et al. (22) documented a decrease in renal plasma flow and GFR following the administration of propranolol that averaged <10% of the control values. The infusion of both metoprolol and atenolol was associated with decrements in GFR and renal plasma flow. Pindolol induced a decrease in GFR and renal plasma flow in subjects with GFR >70 ml/min but had a negligible effect on these variables in subjects with filtration rates <70 ml/min. The administration of acebutolol to groups of patients with varying degrees of renal functional impairment caused modest decrements in GFR in those patients with a GFR exceeding 30 ml/min.

In contrast, the infusion of nadolol has generally resulted in either no change (increase of 7%) or in increments of renal plasma flow. For example, Hollenberg et al. (10) reported a marked dose-related increase in this variable with a maximum of 26%. Subsequently, an investigation conducted by Foley et al. (8) documented a 12% increase in renal plasma flow in response to nadolol given intravenously. In the only study that we are aware of regarding the acute effects of nadolol on GFR, O'Connor et al. (17) failed to demonstrate a significant change following a single oral dose. Penbutolol, a long-acting β-blocker with ISA, did not alter GFR after a single intravenous dose.

Changes in Renal Hemodynamics Associated with Chronic Administration of β-Adrenergic Antagonists

Many of the investigations have involved the use of the prototypical agent, propranolol, the cardioselective long-acting agent, atenolol, and the long-acting medication, nadolol, which is neither cardioselective nor ISA positive.

Considering propranolol, of nine separate determinations (in five papers), GFR declined in six instances and was unchanged in three. Likewise, renal plasma flow decreased in eight of nine instances and was unchanged in one. Of interest, in one of the three studies in which propranolol was not demonstrated to reduce GFR, the protocol involved a sequential trial of nadolol followed by propranolol. The authors interpreted their findings as indicating a protective carry-over effect of nadolol. Similarly, in the only study in which renal plasma flow was not reduced at rest, exercise was followed by a greater decline in renal plasma flow in the propranolol-treated than in untreated patients with essential hypertension.

On the other hand, it is quite clear that these adverse effects are not a universal feature of all β-blockers. For example, Hollenberg et al. (10) demonstrated that the acute administration of propranolol diminished renal blood flow. Conversely, nadolol induced a significant dose-related increment in renal perfusion commencing at the threshold dose that reduced heart rate (Figures 1 and 2). The results of most, but not all, investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is not associated with adverse effects on renal function. For example, GFR decreased in only one of five evaluations and was unchanged in the other four. Renal plasma flow increased in two of five determinations and was unchanged in the other three; i.e., it declined in none. Likewise, for atenolol, GFR declined in only two of six instances and was unchanged in the other four. Renal plasma flow was unchanged in three of four instances and declined in one. Considering four other drugs (alprenolol, acebutolol, penbutolol, and pindolol) as a group, of eight determinations of GFR there were no changes in six, an increase in one, and a decrease in the other. For renal plasma flow there were no changes in four assessments and a decrease in three instances.

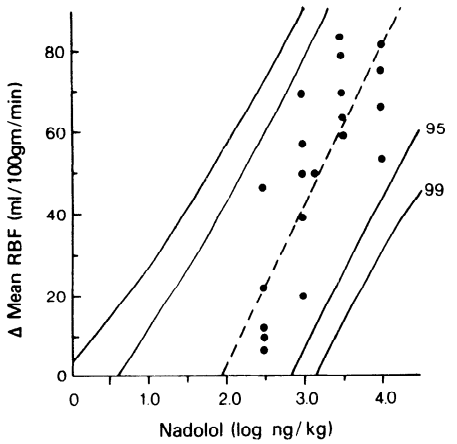

Figure 1
Relationship between nadolol dose and change in mean renal blood flow. The abscissa denotes the logarithm of the nadolol dose and the ordinate the change in mean renal blood flow (△, Mean renal blood flow). As can be seen, nadolol induced a significant dose-related increase in renal blood flow. (Reproduced with permission from Hollenberg, et al., Ref. 10.)

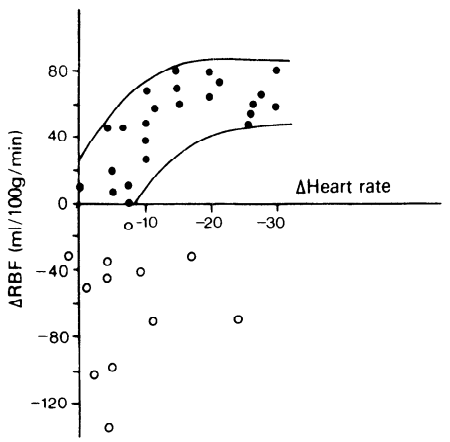

Figure 2
Comparison of relative influence of two β-adrenoceptor-blocking agents, nadolol (•) and propranolol (○), on heart rate and change in renal blood flow (△, Mean renal blood flow). As can be seen, nadolol resulted in an increase in △ mean renal blood flow at the threshold dose that reduced heart rate. (Reproduced with permission from Hollenberg, et al., Ref. 10.)

Discussion

It seems apparent that, in considering the influence of β-antagonists on renal function, the β-blockers should not be considered in toto. Some agents appear to produce different effects from those of others. Thus, whereas the majority of investigators utilizing propranolol have reported decrements in renal plasma flow and GFR, this does not appear to obtain for nadolol or, based on somewhat more limited data, for atenolol and perhaps for some of the ISA-positive medications.

Pathophysiological Mechanism(s) of Adverse Effects of β-Antagonists on Renal Blood Flow and GFR

At this point it is appropriate to inquire why some β-blockers exert an adverse effect on renal perfusion and GFR. The putative mechanisms are a reduction in cardiac output and/or an increase in renal vascular resistance due to several factors.

The relation between antihypertensive medication-induced reductions in cardiac output and reduced renal plasma flow and/or GFR is well known. Although it most likely plays a role in the effect of β-adrenoceptor blockade on renal function, consideration of available data indicates that a reduction in cardiac output cannot constitute the sole or even the major mechanism. Rather, the influence of reduced cardiac output might often be permissive rather than pivotal.

If reduction in cardiac output were the sole explanation for β-blocker-induced perturbation of renal perfusion, a reduction in renal plasma flow might be anticipated in response to virtually every β-antagonist, since with the exception of those exerting ISA all diminish cardiac output to varying degrees. The observations that some β-adrenergic blocking agents do not decrease renal perfusion despite a decrease in cardiac output indicate there must be additional explanations for the hemodynamic changes.

Propranolol-related decrements in cardiac output are associated with increases in both total peripheral resistance and renal vascular resistance. As a result, renal plasma flow and GFR might be expected to decline. On the other hand, Dreslinski et al. (3) reported a decline in renal plasma flow with acebutolol (a cardioselective ISA-positive agent not yet available in the US), even though cardiac output did not change. In this regard, although based on a single report, the discrepant behavior of penbutolol is also of interest. It has been reported that this long-acting β-blocker with ISA did not reduce renal blood flow when given intravenously and increased GFR by 16% when given orally for 6 days. Whether its putative lack of effect on cardiac output, its ISA, its suggested vasodilator properties, or some factor related to its long duration of action are pivotal in the apparent preservation of renal hemodynamics cannot be ascertained at this time. Furthermore, nadolol and atenolol, despite producing similar effects on systemic hemodynamics as propranolol, may exert a quite different influence on renal hemodynamics. Specifically, they may reduce renal vascular resistance and maintain or actually increase the percent of cardiac output delivered to the kidney [Textor et al. (25)]. For example, in one study, chronic nadolol administration was associated with a 30% increase in renal plasma flow despite a 21% decrement in cardiac output. This phenomenon has been referred to as a buffering of the renal circulation from the effect of decreased cardiac output.

Let us now consider the alterations in renal vascular resistance. Such an increase might be attributable to *1*) an initial response to a decrement in cardiac output; *2*) increased activity of the α-adrenoceptor system in the renal vasculature; *3*) a direct renal action, independent of adrenergic or hormonal mechanisms; *4*) an alteration of renal vasodilatory mechanisms.

In summary, the mechanism of β-blocker-induced alteration of renal plasma flow and GFR is almost certainly hemodynamic, rather than nephrotoxic. The pathophysiological factors appear to be multifactorial and variable, and the end result relates to diminished cardiac output, increased renal vascular resistance, or both (Figure 3). It is possible that inhibition of renal vasodilators, such as the kallikrein-kinin system, also plays a role.

Why do some, but not all, β-blockers appear to increase renal vascular resistance? An acute reduction of

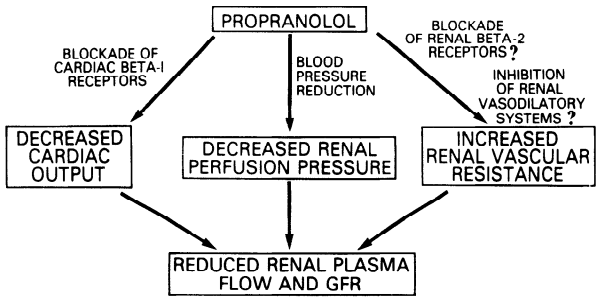

Figure 3
Postulated mechanisms for β-blocker-induced impairment of renal hemodynamics. Factors, as exemplified by propranolol (which has been most intensively studied), appear to be multifactorial and variable. Among the most important of these are blockade of β_1-receptors with the resultant effect on heart and blood pressure and blockade of renal β_2-receptors with its influence on renal vascular tone. The latter might also be adversely affected by inhibition of renal vasodilators (such as kallikrein-kinin system) and/or by the myogenic response to reduced cardiac output. Interacting pathophysiological "final pathways" almost certainly involve diminished cardiac output, reduced renal perfusion pressure, and increased renal vascular resistance.

cardiac output tends to increase total peripheral resistance, at least in part as a result of α-adrenergically mediated reflex vasoconstriction. With the chronic use of propranolol, total peripheral resistance returns toward, but not below, the pretreatment level. Whereas an initial increase in renal vascular resistance might merely reflect an intrinsic myogenic response of arteriolar smooth muscle in the peripheral circulation, including that of the kidney, to decreased perfusion pressure, it seems unlikely that the chronic response is explainable on this basis. The observation that renal plasma flow may decrease after chronic propranolol administration even when there is no change in mean blood pressure has been used to underscore the point that renal plasma flow may vary independently of blood pressure. On the other hand, Brater et al. (2) have recently reported the absence of adverse renal hemodynamic effects following the longterm administration of propranolol to 18 black patients, only two of whom had therapeutic blood pressure responses. The investigators concluded that in the absence of blood pressure reduction, β-blockade per se has no deleterious effect on renal function.

Alternatively, it has been suggested that the adverse renal response to propranolol might reflect a local intrarenal effect rather than a systemic one. The infusion into the renal artery of doses of propranolol that are too small to produce a systemic effect reduce renal perfusion. Similarly, the intravenous administration of propranolol has been shown to produce renal vasoconstriction in doses insufficient to reduce either heart rate or cardiac output. Since there is reasonable evidence that the renal vasculature possesses β-receptors, it may be that propranolol blocks the β_2-adrenoceptors, leaving α-receptor-mediated vasoconstriction relatively unopposed. Of interest, a preliminary observation suggests that under certain conditions propranolol might directly stimulate α-receptors. An analogy could be drawn with β-blocker-induced worsening of peripheral vascular disease, which appears to be more likely in patients with a vasospastic component to their disease.

As mentioned earlier, renal vascular resistance tends to increase in untreated essential hypertension. If some of this increase is mediated by circulating catecholamines or by alteration of the activity of the autonomic nervous system, the administration of a β-blocker might result in a further increment in vascular tone. This hypothesis is also consistent with the findings of Pedersen (19, 20). He noted that in his young patients with early essential hypertension, renal hemodynamics were unchanged or slightly reduced. Nevertheless, the reduction of GFR and renal plasma flow during exercise was more pronounced in the propranolol-treated than in the untreated group. Pedersen (19) proposed that the apparent fall in the blood supply to the kidneys in propranolol-treated patients could be secondary to vasoconstriction caused by an exercise-induced increase in α-adrenergic stimulation.

It should be mentioned that the increase in renal vascular resistance associated with the use of β-blockers might be mediated independently of any effect on the β-adrenergic system. For example, these medications might have a direct effect on the renal circulation or depress the activity of normal vasodilatory mechanisms such as the prostaglandin or kallikrein-kinin systems.

In summary, it appears likely that β-blocker-induced alteration of renal perfusion is modulated at least in part by vasoconstriction mediated by α-adrenoreceptors. These are probably responding either to a decrease in cardiac output or, in the context of β_2-receptor blockade, to direct α-receptor stimulation.

Relation Between Changes in Renal Plasma Flow and Those in GFR

In an attempt to ascertain the relationship between the reduction in renal plasma flow and that of GFR we considered those studies in which simultaneous determinations were made of *both* renal plasma flow and GFR before and during the administration of propranolol. In each of the three instances in which GFR was reduced by >10%, renal plasma flow was also decreased by a similar percentage. On the other hand, renal plasma flow was reduced in six instances, i.e., in three additional assessments. In a study using another agent, alprenolol, it was reported that a 13% decrement in GFR was accompanied by a 23% decrease in renal plasma flow. These observations are certainly more consistent with a hemodynamic rather than a nephrotoxic pathogenesis for the change in GFR.

Mechanism for Variable Effect of Different β-Blockers on Renal Hemodynamics

Why should propranolol appear to have consistently adverse, albeit rather small, effects on renal function, whereas other β-blockers such as nadolol, apparently atenolol, and others tend to manifest these actions much less frequently?

Cardioselectivity

One consideration is that cardioselectivity might confer protection against renal vasoconstriction because of a lesser tendency to inhibit the putative renal vascular β_2-receptors. There is substantial evidence to support such a formulation. Many, but not all, studies concerned with the chronic use of cardioselective agents have shown a relative preservation of renal hemodynamics in

comparison to the alterations associated with the use of propranolol.

The property of cardioselectivity is dose related. It might be therefore anticipated that if cardioselectivity were the important feature, the protection of hemodynamics might diminish with the higher doses. Unfortunately, an examination of dosages in the various studies using cardioselective agents does not provide clarification of this issue. Nevertheless, Wilkinson et al. (29) utilized an average dose of atenolol of ~220 mg (the clinically recommended dose is generally up to 100 mg) and observed no decrease in GFR. On the other hand, a total daily dose of atenolol of 200 mg, which is relatively high, was associated with a decrease in creatinine clearance in two of three groups of subjects studied by Zech et al. (30). Perhaps the most compelling evidence militating against cardioselectivity being the major factor is the finding that nadolol, the β-antagonist most associated with preservation of renal hemodynamics, is not cardioselective.

Intrinsic Sympathomimetic Activity

The property of ISA might also confer protection from decreased renal plasma flow and GFR. This could relate to a lesser or absent decrement in cardiac output or, conceivably, to a component of preferential sympathomimetic effect within the renal circulation. We have reviewed the renal hemodynamic data from six studies of patients chronically receiving agents with varying degrees of ISA. Only one of the agents, acebutolol, is considered to be cardioselective. Of seven determinations of renal plasma flow, there was no change in four and decrements exceeding 10% (of 12, 16, and 23%) in three. Of nine determinations of GFR, there was no change in seven, an increment of 16% in one, and a decrement of 13% in the other. Renal vascular resistance was determined in four instances and was unchanged in three and decreased in one. In the last-mentioned case, renal plasma flow had not changed, whereas in two of the other three circumstances renal plasma flow decreased by 12 and 16%. Unfortunately, data for cardiac output were not routinely provided by the investigators. In summary, these observations as well as those of more recent studies support the impression that medications with ISA, unlike propranolol, do not consistently produce an adverse effect on renal plasma flow and only rarely reduce GFR.

Nadolol

The apparent discrepant tendency of nadolol to maintain renal plasma flow and GFR in spite of the absence of either cardioselective or ISA properties is of great interest. Like atenolol and in contrast to propranolol, nadolol is relatively water soluble. There is no apparent reason, however, why water solubility might relate to a differential effect on renal function. Of note, there is some evidence that nadolol, in contrast to other β-blockers, might have dopaminergic properties that could either confer a vasodilatory effect or offset the influences on the renal vasculature of β-blockade. Likewise, there is preliminary evidence suggesting that nadolol, as opposed to propranolol, does not suppress the renal production of vasodilatory kinins.

In summary, the pathogenesis of decreases in renal plasma flow and GFR in response to β-blocking agents is uncertain. It is therefore not surprising that the explanation as to why some of these agents do not consistently diminish these variables is unknown. Individual medications may differ in their effect on intrarenal vascular receptors, renin secretion (and presumably local angiotensin II generation), cardiac output, blood pressure, and possibly in the potential for a direct effect on the renal vasculature. Thus the mechanism of protection conferred by an agent may be multifactorial and differ from that of another β-blocker (Figure 4). For example, nadolol might protect by inducing direct or indirect vasodilation; atenolol by producing relatively less β_2-receptor blockade (or no direct α-receptor stimulation), and pindolol because of its ISA property with resultant maintenance of cardiac output and possibly by virtue of a lesser net inhibition of β-receptors. Similarly, it is tempting to speculate that labetalol (the newly released antihypertensive agent that blocks both α- and β-adrenoceptors) might exert a protective effect on renal vascular resistance by virtue of either its α-adrenergic inhibition or its postulated β_2 stimulatory activity.

Plasma volume

Although an early report suggested that propranolol tends to decrease plasma volume, this observation has not been borne out by more recent studies. Thus contraction of intravascular volume cannot be considered as a factor involved in the reduced renal hemodynamics associated with the use of β-blockers.

Influence of Dose

There are insufficient data to determine whether differences in the dosage of β-blockers relate to the tendency to reduce either renal plasma flow or GFR. Many of the investigators titrated the dose of β-antagonists to achieve blood pressure control so that the dosage varied from patient to patient. Although Bauer and Brooks (1) utilized a variety of dosages, the study was done sequentially without a washout period, and no conclusions can be drawn.

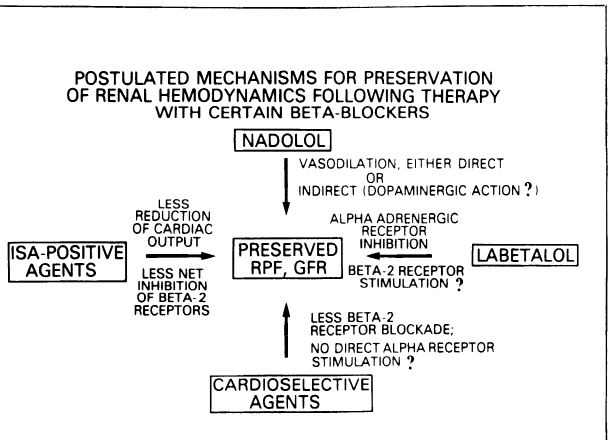

Figure 4
Postulated mechanisms for preservation of renal hemodynamics following therapy with certain β-blockers. It is likely that the mechanism of "protection" conferred by a specific medication differs from that provided by another agent. Thus nadolol might induce direct or indirect vasodilation; and cardioselective agent, atenolol, might produce relatively less β_2-blockade (or no direct α-receptor stimulation). Pindolol, an ISA-positive medication, tends to preserve cardiac output and because of its partial agonist activity might provide less *net* inhibition of β-receptors. Finally, aside from its maintenance of cardiac output, labetalol might cause intrarenal α-adrenergic receptor inhibition or, possibly, partial β_2-receptor stimulation.

Influence of Duration of Therapy

Inadequate information is available to draw any conclusions on this topic. In the various studies, duration of therapy ranged from a few weeks to more than 6 months, and no consistent picture emerges. Only a few investigators measured renal function sequentially during therapy. In the study of Bauer and Brooks (1) the dose of propranolol was changed weekly confounding interpretation. In the study of Ibsen and Sederberg-Olsen, (11) the changes in GFR were similar after 2–3 and 4–5 months. Likewise, Falch et al. (6) reported that the renal plasma flow after 8 months of therapy with propranolol, which was 23% below the untreated level, was not significantly different from the value noted after 1 month of treatment (15% below the base-line level).

Comparison of Effect of β-Blockers on Renal Function with That of Other Antihypertensive Medications

All medications that lower blood pressure do not reduce renal plasma flow or GFR, but when cardiac output is reduced the chance of a detrimental effect on renal function is increased. Of interest, preservation, or even improvement in renal perfusion despite reduction in mean arterial blood pressure, has been observed by Warren et al. (27) not only with hydrochlorothiazide and furosemide but also with the sympatholytic drugs clonidine and prazosin as well as with the combination of guanabenz and hydrochlorothiazide. In contrast, these investigators observed a propranolol-induced decrease in GFR and renal plasma flow. Similarly, Falch et al. (7) observed no change in renal plasma flow associated with the use of hydralazine but reported a decline in that variable when hydralazine was withdrawn from a regimen consisting of hydralazine plus propranolol. Finally, O'Connor et al. (18) observed preservation of renal hemodynamics with prazosin but not with propranolol. Obviously, these findings support the impression that reduction in perfusion pressure can not be the primary variable influencing renal hemodynamics. Rather, a multifactorial modulation that may include, for example, alteration of cardiac output, an effect on β_2- and/or α-adrenoceptors in the kidney, and a direct effect on the renal vasculature appears to be operative.

Effect of β-Adrenergic Antagonists on Renal Hemodynamics During Exercise

Studies carried out in the basal state at rest may not necessarily reflect all the hemodynamic perturbations associated with the use of medication. Of note, Pedersen (20) reported only slight changes in renal hemodynamics induced by propranolol when the subjects were at rest, whereas renal plasma flow was lower during exercise in association with propranolol administration than prior to therapy. In a subsequent paper, Larsen and Pedersen (13) demonstrated that the reduction in renal plasma flow and GFR during exercise was greater in propranolol-treated patients than in a separate group of untreated hypertensives.

Protection by Vasodilator

If propranolol compromises renal perfusion by increasing renal vascular resistance, a vasodilator might be expected to provide protection against propranolol-induced decrements in renal perfusion. Insufficient data are on hand to resolve this question, but in a single study Falch et al. (7) noted that the addition of propranolol to a regimen consisting of hydralazine alone was not associated with any alteration of renal plasma flow. From a practical point of view, the lack of any detrimental effect of renal hemodynamics of the combined α and β-blocker, labetalol, might be attributable to the indirect vasodilation provided by β-blockade.

Reversibility of Effect

In an oft-cited paper, Bauer and Brooks (1) noted that 2 months after the discontinuation of propranolol the renal plasma flow of their patients had returned to the baseline level. In contrast, the inulin clearance remained significantly less than that documented prior to therapy. Based on this observation, the authors suggested that the adverse effect of propranolol on GFR might be only slowly or incompletely reversible. In contrast, Ibsen and Sederberg-Olsen (11) showed that the ^{51}Cr-ethylenediaminetetraacetate (EDTA) clearance was significantly higher (by 16%) 2 months after the discontinuation of propranolol than it was at the end of 4 months of therapy. It should be noted, however, that in this study the GFR had not been measured prior to therapy. Surprisingly, in the 11 other investigations using propranolol that we reviewed, no evaluations of reversibility were reported. Obviously, there is a need for this important issue to be answered by appropriate studies.

Effect of Suppression of Plasma Renin Activity

Since in sodium-depleted states activation of the renin-angiotensin axis tends to decrease renal plasma flow, suppression of plasma renin activity might tend to increase renal plasma flow by decreasing the activity of the potent vasoconstrictor substance, angiotensin II. Theoretically, therefore, β-blockers that fail to decrease plasma renin activity might tend to impair renal function. Nevertheless, there does not appear to be any relationship between alteration in plasma renin activity and changes in renal plasma flow. Generally, propranolol suppresses plasma renin activity as does atenolol and nadolol; yet the effects of these agents on renal plasma flow are frequently different. Similarly, nadolol sometimes exerts no effect on plasma renin activity but tends to maintain renal plasma flow.

It must be emphasized that the issue regarding the renin-angiotensin-aldosterone axis is exceedingly complex. We have just discussed the possibility that a decrease in plasma renin activity might confer protection against a decline in renal plasma flow. On the other hand, captopril may exert a deleterious effect on renal hemodynamics in patients with bilateral renal artery stenosis. It is therefore possible that propranolol reduces GFR by attenuating angiotensin-modulated autoregulation. Such an action, however, would not account for the decrement in renal plasma flow per se.

Influence of Preexisting Renal Insufficiency on Renal Response to β-Blocker

Most controlled studies evaluating the effect of β-blockers on renal function have studied patients with normal or near normal renal function. Thus there are insufficient data to ascertain whether β-blocker-related decrements in renal hemodynamics are greater in subjects with underlying renal failure. Nevertheless, the findings of Zech et al. (30), though preliminary, are of

interest. These workers noted that the decrease in creatinine clearance (27%) in nine subjects with a baseline creatinine clearance of <35 ml/min was similar to that of volunteers whose clearance was >75 ml/min (25%). Unexplainedly, their 16 subjects with an initial creatinine clearance between 35 and 75 ml/min demonstrated only a 7% decrement. Obviously, this area requires further study.

Methods for Estimation of GFR

In view of the disparate reports on the effects of β-blockers on renal hemodynamics, one might ask if such discrepancies might relate in part to differences in methods and not represent true variability.

Bauer and Brooks (1) commented that creatinine clearance data might not accurately convey the true changes in GFR reflected by inulin clearance (change in C_{In} – 27%, C_{Cr} – 11%, true C_{Cr} – 14%). To ascertain the validity of such an assertion we examined the other studies in which creatinine clearance was measured simultaneously with that of an additional methodology. In patients studied by Waal-Manning and Hobson (26) receiving nadolol, the change in creatinine clearance was +4% and with ^{51}Cr-EDTA + 8%. In another study utilizing nadolol, O'Connor et al. (17) reported a 5% decrease in creatinine clearance and a 4% increase in inulin clearance. Finally, Wilcox et al. (28) found a 9% decrement in GFR using ^{51}Cr-EDTA and no change (0%) with creatinine clearance. Thus the data are very limited and, except for the study of Bauer and Brooks (1), do not relate to propranolol. There is at present insufficient evidence to support the claim that creatinine clearance methodology is insufficient to discern the nature of a change in GFR in patients receiving β-antagonists. Clearly, from the clinician's point of view, the readily available creatinine clearance suffices.

Clinical Importance of β-Blocker-Induced Alteration of Renal Perfusion

One must inquire whether β-antagonist-related perturbations of renal hemodynamics have clinical importance. Although the available data do not permit a definitive answer, we believe that the answer at this juncture should be a qualified yes. First, such hemodynamic alterations may contribute to the reduced capacity of patients receiving propranolol to handle a sodium load. Conceivably, the resultant sodium retention could limit the antihypertensive effects of the drug. Second, when renal function is already marginal, a further reduction in glomerular filtration rate may be detrimental, at least in some patients. Only scattered case reports of very small numbers of patients, however, have been cited as evidence that β-blockers cause a deterioration of renal function and/or precipitate uremia. On the other hand, a very large clinical experience over many years has failed to indicate an apparent adverse clinical effect. Finally, it is clear that β-blockers are extremely valuable antihypertensive agents.

Some β-blockers do not produce a categorical effect on the kidney, and some agents such as nadolol (and perhaps atenolol and others) may preserve or even augment renal perfusion. This raises the possibility that in some patients the choice of a β-blocker in the future may be predicated on its potential salutary effect on the renal circulation.

Renal β-Receptor and Renin Release

Just as β-blockers exert differing and at times diametrically opposite effects on renal hemodynamics, the effects on renin release are similarly complex.

The juxtaglomerular apparatus has a rich sympathetic nerve supply, and universal agreement has been reached that one of the factors determining renin release from the kidney is the sympathetic nervous system. Isoproterenol and epinephrine, the most active catecholamines in activating the β-adrenergic receptor, both promote brisk renin release; moreover, the most widely employed β-adrenergic blocking agent, propranolol, effectively blunts renin release.

Three broad questions have been raised by a number of investigators. First, is the renin-releasing action of catecholamines exerted within the kidney directly on receptors in the juxtaglomerular apparatus, or does it reflect an alternative intrarenal or systemic response to the β-adrenergic action? Second, is the action of propranolol specifically related to its β-adrenergic blocking action? Third, is the pertinent β-adrenergic receptor subtype in the β_1 category, as might be anticipated, or is a β_2 or an alternative receptor involved?

A number of lines of evidence indicate that the renin-releasing action of catecholamines is exerted directly on a β-adrenergic receptor within the juxtaglomerular apparatus. Nevertheless, a serious question concerning the intrarenal role was raised by Reid et al. (21), who considered the dominant effect to be via the systemic effects of the β-agonists. Furthermore, the interpretation of many experiments has been complicated by additional intrarenal actions of these agents on renal hemodynamics and on renal sodium handling and, thus, potentially on sodium delivery to the macula densa. Nerve stimulation, however, led to renin release in the nonfiltering kidney treated with papaverine, a preparation in which sodium handling is thought to be inoperative. In addition, renin is released from the isolated kidney perfused with isoproterenol, as well as from kidney slices when epinephrine and isoproterenol have been added to the incubation medium. Although in many experiments the concentrations of catecholamines employed were very high, renin release occurs when more reasonable and probably when physiological concentrations are employed. Taken together, the evidence suggests that any hemodynamic or alternative intrarenal effect of the β-adrenergic mediators might add to, but are not fundamental to, the response: a major action clearly lies within the juxtaglomerular apparatus itself.

What of the specificity of propranolol? When the response to stimuli provoking renin release is influenced by propranolol, does that necessarily indicate that nervous system mechanisms acting via β-receptors are involved? D-Propranolol has all of the properties of the L-form except for a sharp reduction in its capacity to block β-adrenergic receptors; this agent does not block renin release in vitro in the isolated perfused kidney, in experimental animals, or in humans. Maneuvers that are thought not to involve the nerve supply when they promote renin release, such as the response to large doses of furosemide or to reduced renal perfusion pressure, are not influenced by doses of propranolol that block the renin-releasing effects of stimulation of the renal nerves. In sum, the available evidence suggests that

when propranolol blunts renin release, it does so by way of its specific action of the β-adrenergic receptor.

What is the nature of the β-adrenergic receptor subtype involved? Here the answer is less clear. Lands (12) originally defined the receptor subtypes on the basis of their relative response to epinephrine and norepinephrine. For the β_1-receptor subtype, typified by cardiac responsiveness and lipolysis, norepinephrine and epinephrine were equi-effective. On the other hand, for the β_2-receptor subtype, typified by vasodilator and bronchial smooth muscle relaxation, epinephrine was much more effective than norepinephrine in stimulating a response. Since it is very likely that the neural hormone released is norepinephrine, it is fortunate that the β_1-receptor, the one that is innervated, should be sensitive to norepinephrine. On that basis, because it seems likely that it is the nerve supply to the juxtaglomerular apparatus that is responsible for renin release, one would have anticipated that the receptor subtype involved in renin release should be β_1. By the late 1970's, however, sufficient evidence had accumulated favoring the β_2-receptor that several reviewers came to a counterintuitive conclusion. That is, despite compelling a priori reasons for anticipating that a β_1-receptor was involved and mixed evidence, they concluded that a β_2-receptor was involved.

Examination of the results of experiments that employed Lands' (12) original criteria is instructive. According to Lands' (12) hypothesis, if the β-receptor subtype involved were β_1, one would anticipate that norepinephrine would be as effective as epinephrine in mediating renin release. This is clearly not the case; a host of studies have shown that norepinephrine is either less effective than epinephrine or, indeed, may blunt renin release. The response to norepinephrine, of course, is complicated by action on the renal vasculature.

There are several approaches to define the β_1- and the β_2-receptor. Lands' (12) original criterion, as described above was the relative potency of norepinephrine and epinephrine. Subsequently, a series of β_1- and β_2-agonists and antagonists have been developed and widely employed to assess β-receptor subtypes. Unfortunately, none provide the substantial separation in dose-response curves that have been so helpful in identifying and separating α- and β_1-receptors: they are characterized by relative, not absolute, selectivity.

Thus the situation has not been clarified by the use of the relatively selective β_1- and β_2-agonists and antagonists that have been employed. Studies with these agents have provided evidence favoring both β_1 and β_2 mechanisms.

Species differences may have contributed to the confusion. A large number of studies in the dog have revealed the importance of β_1 subtype in this species. Even here studies with the relatively selective agents have on occasion suggested a β_2 subtype. Mixed evidence has also been presented in the rabbit, rat, and cat. Several investigators, recognizing these difficulties, have suggested that the β-adrenergic receptor subtype mediating renin release may be neither β_1 nor β_2.

What of man? Many of the studies possible in animals have not yet been carried out in humans, but the bulk of available evidence favors a β_1-receptor subtype. On the other hand, some experiments have provided evidence favoring a β_2-receptor subtype.

The conclusion that the adrenergic control of renin release in humans is complex is supported by recent studies with sotalol. This agent, a nonselective β-adrenergic blocking agent free of intrinsic sympathomimetic activity, promoted renin release both in vitro and in humans. The fact that it acts as a partial agonist in terms of renin release, but a pure competitive antagonist with regard to its cardiac effects, strongly favors a β-adrenergic receptor that differs in two areas. The receptor mediating renin release may, indeed, resemble the β_1-adrenergic receptor in the myocardium but differ sufficiently to raise problems with classification.

Why should the β-adrenergic receptor differ in various regions? Sokabe (23) has organized the information on the phylogeny of renin release, documenting that the potential for renin synthesis and release occurs very early in phylogeny. Although no data directly dealing on this subject appear to be available, it may well be that the β-adrenergic receptor in the juxtaglomerular apparatus is equally primitive. The phylogeny of the catecholamine receptors responsible for renin release might be a fruitful place to dissect the mechanisms involved.

Are there any implications for therapy? At the moment the answer is probably no, but it is not difficult to envision the development of β-adrenergic blocking agents that have a marked influence on renin release, though influencing other β-adrenergic receptors substantially less.

Implications and Conclusions

1) There is a paucity of information on the *acute* effects of β-blockers on renal hemodynamics in humans, and the relationship of these acute changes to the *long-term* alterations is uncertain. Of note, only nadolol has been reported to produce *increments* in GFR and/or renal plasma flow.

2) In general, the *chronic* use of propranolol for the management of hypertension is characteristically associated with decrements of renal plasma flow and glomerular filtration rate, generally in the range of 10–20%. This contrasts with the usual lack of any significant long-term effect on renal function of the use of some of the other classes of antihypertensive agents (particularly diuretics and vasodilators) including some of the other sympatholytic medications. Except for nadolol and, perhaps certain cardioselective and ISA-positive agents, no definite statement can be made regarding renal effects of the various other β-blockers.

3) The results of most, but not all, investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function. The reason(s) for this discrepant property in comparison to propranolol is unknown and requires further study.

4) Theoretically, cardioselective and ISA-positive β-adrenergic inhibitors might produce less renal vasoconstriction than nonselective agents. The data pertaining to atenolol, and to a lesser extent some of the other pertinent medications, appear to support this premise, at least with regard to GFR, but additional information is necessary.

5) There is no evidence that β-blockers are directly nephrotoxic. Rather, the mechanism of their alteration of renal plasma flow and glomerular filtration rate is almost certainly hemodynamic. The exact pathophysiol-

ogy is unknown but appears to be multifactorial and variable, probably relating either to diminished cardiac output or to increased renal vascular resistance, or both. It is possible that inhibition of renal vasodilators such as the kallikrein-kinin system plays a role.

6) With chronic use the adverse hemodynamic effects of β-blockers appear to persist for the duration of therapy.

7) At this time, the data are insufficient to indicate whether or not such factors as the chronicity of hypertension, preexistence of renal insufficiency, concomitant use of other medications, dose of β-blocker, duration of therapy, status of extracellular fluid volume, or the age of the patient predispose to β-blocker-induced decrements in renal hemodynamics.

8) The clinical implications of β-blocker-induced renal changes are presently unknown. The alterations do not appear to be of major importance in patients with normal renal function. A very large worldwide clinical experience over a period of two decades has failed to indicate an apparent important adverse effect. Even in patients with underlying renal insufficiency, we see no reason at this time to proscribe the use of β-adrenoceptor blockers. Rather, one should monitor renal function by serum creatinine levels and, when appropriate, by more discriminating determinations.

9) If renal function is noted to decline during chronic therapy with propranolol, the physician may consider changing therapy to either nadolol, or perhaps an ISA-positive or cardioselective agent. Alternatively, an entirely different type of medication such as prazosin, hydralazine, clonidine, or, when necessary, minoxidil or a calcium channel blocker may be selected.

10) There is an important need for large-scale, cooperative, prospective, controlled, long-term studies evaluating the chronic effect of all of the currently marketed β-blockers, particularly those that appear to preserve renal function. Several acceptable clearance techniques for the determination of renal plasma flow and glomerular filtration rate should be used. Post-discontinuation studies to answer the question of reversibility are also necessary.

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β-Blockers and the Kidney
Multiple Choice Questions

For all of the following questions choose the *single best* answer.

1. Which *one* of the following β-blockers is considered highly water soluble?
   a. propranolol
   b. metroprolol
   c. nadolol
   d. pindolol
   e. timolol
2. Which *one* of the following β-blockers is considered beta-1 selective?
   a. propranolol
   b. metoprolol
   c. nadolol
   d. pindolol
   e. timolol
3. Which *one* of the following *best* characterizes the hemodynamic consequences of untreated, asymptomatic, chronic essential hypertension?
   a. increased cardiac output, increased peripheral resistance
   b. decreased cardiac output, decreased peripheral resistance
   c. increased peripheral resistance and a cardiac output that may be normal at rest, but is usually low during muscular exercise
   d. frankly decreased cardiac output, increased peripheral resistance
   e. increased cardiac output, decreased peripheral resistance
4. Possible mechanisms of β-blocker-induced increments in renal vascular resistance include all of the following (*a–d*) *except*:
   a. increase in *a*-adrenergic tone related to a fall in cardiac output
   b. increase in *a*-adrenergic tone related to a decrease in stimulation of arteriolar β_2-receptors
   c. perturbation of vasodilatory mechanisms such as the kallikrein-kinin system
   d. a direct vasoconstrictive effect
   e. all of the above
5. Which *one* of the following statements (*a–d*) concerning β-blocker-induced reduction in renal plasma flow (RPF) and GFR is *incorrect*?
   a. all β-blockers appear to manifest a similar tendency to produce adverse effects
   b. in general, any decrease in RPF or GFR is in the range of 10–20%
   c. it is likely that the changes have a hemodynamic rather than a direct nephrotoxic basis
   d. several studies have shown that the long term use of nadolol (and perhaps some of the cardioselective and ISA-positive agents) is generally not associated with perturbation of renal function
   e. all of the above are incorrect
6. Which *one* of the following statements (*a–c*) concerning the hemodynamic effect of administration of β-blocker to a patient with essential hypertension is *incorrect*?
   a. when a single oral dose of propranolol is given, an increment in peripheral resistance counterbalances the decrement in cardiac output, and the BP is unchanged.
   b. with the chronic use of propranolol, the cardiac output is reduced, and the peripheral resistance is either close to the base-line level or above it
   c. with the chronic use of a potent ISA-positive agent, such as pindolol, the cardiac output is close to the base-line level, and the peripheral resistance is reduced
   d. all of the above are correct
   e. all of the above are incorrect
7. Which *one* of the following (*a–d*) is *correct*?
   a. it has been clearly established that renin release is modulated by β_1-receptors
   b. stimulation of the β_1-receptor causes bronchodilation, arteriolar vasodilation, glycogenolysis, and enhanced lactate production
   c. stimulation of the β_2-receptor causes an increased heart rate, increased myocardial contractility, and enhanced electrical conduction
   d. intrinsic sympathomimetic activity (ISA) refers to the property of simultaneously blocking a β-adrenoceptor yet acting to stimulate partially either the same of other β-receptors
   e. none of the above are correct
8. Which one of the following statements (*a–c*) is *correct*?
   a. all β-blockers that decrease cardiac output do not necessarily decrease renal plasma flow and GFR
   b. a very large experience over many years has failed to indicate a clinically important adverse renal effect of β-blockers
   c. typically, when β-blockers reduce GFR, RPF is also reduced
   d. all of the above are correct
   e. all of the above are incorrect
9. Which *one* of the following antihypertensive medications does *not increase* total peripheral resistance?
   a. clonidine
   b. methyldopa
   c. propranolol
   d. minoxidil
   e. nifedipine
10. Which *one* of the following (*a–d*) is *not* an expected consequence of β-blockade with propranolol in a normal volunteer?
    a. slowing of the heart rate
    b. absence of peripheral edema
    c. increase in stroke volume at rest
    d. absence of marked change in plasma volume
    e. all of the above are expected
11. Which *one* of the following (*a–d*) *best* characterizes the changes in renal hemodynamics associated with chronic, asymptomatic essential hypertension?
    a. a progressive decrease in renal vascular resistance and a progressive increase in renal blood flow
    b. a progressive decrease in renal vascular resistance and a progressive decrease in renal blood flow
    c. relative constancy of GFR with a progressive increase in filtration fraction
    d. a progressive decrease in filtration fraction
    e. none of the above