THE PHYSIOLOGIST

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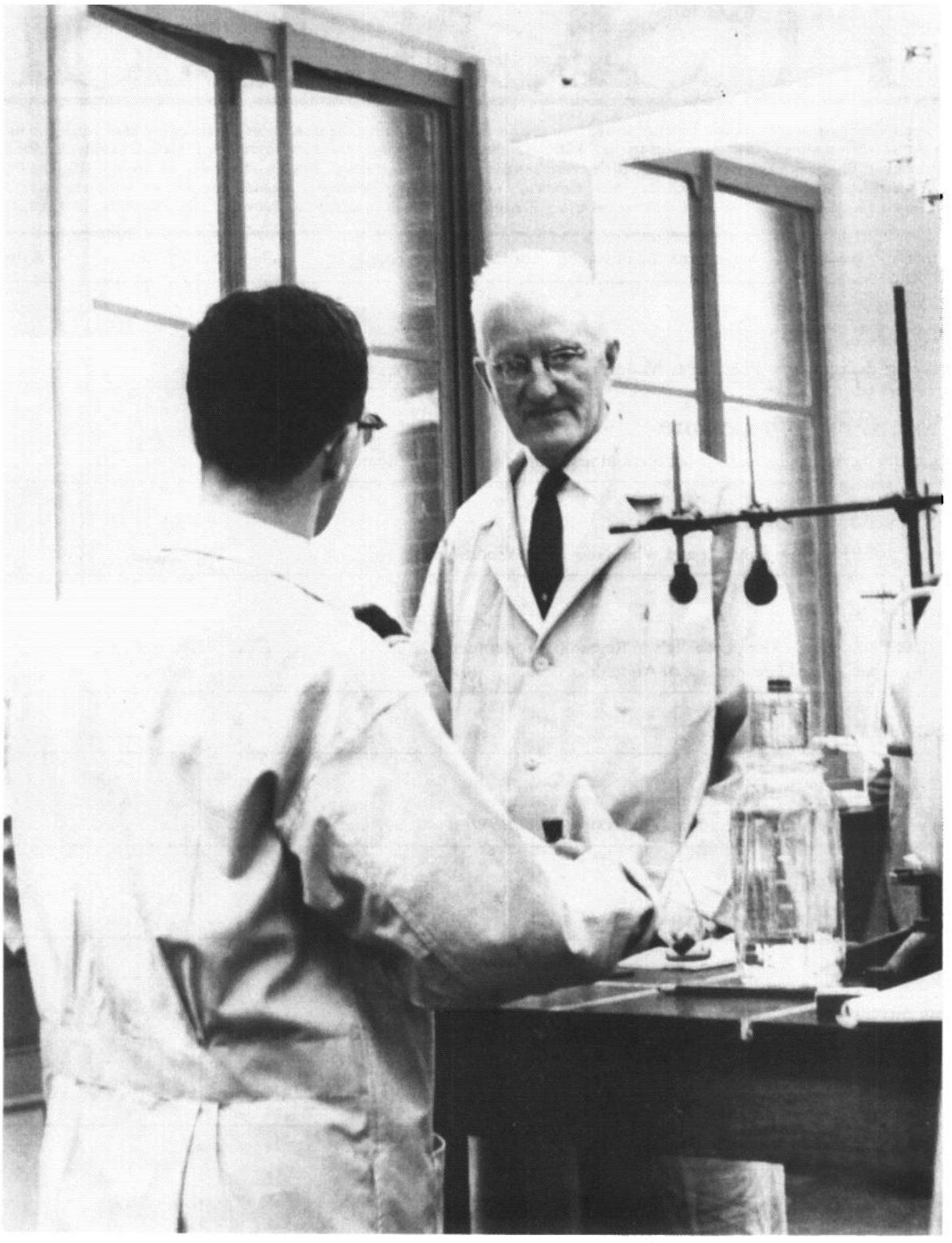
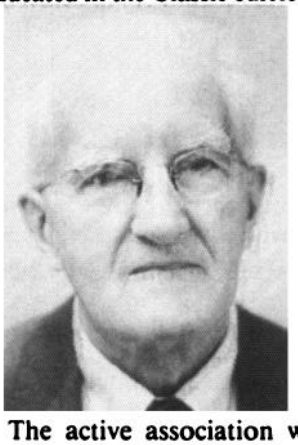


Edward F. Adolph

Edward F. Adolph, the 26th individual elected to the Presidency of the American Physiological Society, was educated in the Classic curriculum—Latin, Greek, philology, and mathematics. His thorough grounding and excellence in these subjects won him a place at Harvard College, where he received his baccalaureate in 1916, followed by two years at Yale. After a year in the US Army Medical Department during World War I, he returned to Harvard to work on his doctorate with the guidance of L. J. Henderson.



The active association with Henderson was briefly renewed in 1936. Edward Adolph often recalls the intellectual stimulation of Henderson whom he characterized as "a self-made intellectual in a university that valued individuals... (and a person) who had an intense faith in man's capacity to comprehend empirical systems both inorganic and living and social (Fitness, Order, Interrelations)." These are precepts that inspired Edward Adolph and best describe his research contributions as well as the man.

However, as he readily admits, life's course through Academia was a bit more existential. After a year abroad as a Sheldon Traveling Fellow at Oxford in 1920 where he studied with J. S. Haldane, he joined the faculty of the University of Pittsburgh. In the same year he married Mary Grace Bagg. He was born in Philadelphia, and both of them spent summers in the Delaware Water Gap country. It was to Bushkill, Pennsylvania, that they returned each summer with their children, Jean, Ruth, and Carl.

During his three years at the University of Pittsburgh, summers were spent at Woods Hole Marine Laboratory. There, young biologists who faced heavy teaching loads, often in one-man departments, met and encouraged one another in their research pursuits. For a year in 1924 he was a Fellow of the National Research Council at Johns Hopkins University.

During the more than 50 years that followed, he has been associated with the University of Rochester, where in 1924 Wallace Fenn had formed a new Department of Physiology. Edward Adolph's students at the University of Rochester included medical, graduate, and undergraduate. He was at his best in the student laboratory where his challenging and insightful questions stimulated many to find answers by performing additional experiments. Sixteen graduate students received a Ph.D. degree with his sponsorship. A large number of medical students and postdoctoral fellows also received special education in his laboratory. In 1975 the Edward F. Adolph Award was established in his honor at the University of Rochester to be awarded annually to a medical student whose accomplishment was judged to be superior.

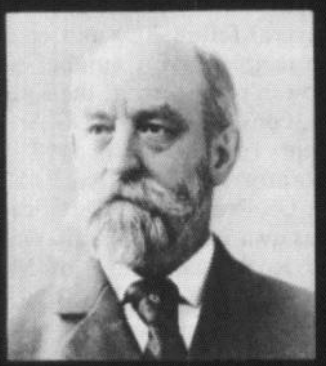
He also held several fellowships and consultantships and has been the recipient of a number of awards: a Guggenheim Fellowship to study at the Kaiser Wilhelm Institute in Berlin, consultant to the US Army Quartermaster Department from 1943 to 1953 and to the Aeromedical Laboratory of the US Air Force in 1944. In 1948 he received a US Presidential Certificate of Merit, and in 1964, he was awarded the Alumni Gold Medal of the University of Rochester School of Medicine and Dentistry. In 1975 he was honored as the University of Rochester's twenty-first John R. Murlin Lecturer.

Edward Adolph recognized early in his researches the significance of regulatory controls, concepts that have been adopted by many of today's bioengineers. His book on *Physiological Regulations* of 1943 has become a classic in the field of regulatory physiology as are his publications on the role of water in living organisms, physiological regulation of body fluids, body size, and body temperature. He has also published studies on development of regulations and adaptations in animals, self-regulation of heartbeats, and other characteristics. There are discussed in his monograph, *Origins of Physiological Regulations*.

In an address as President of the American Physiological Society he reflected on what it means to be a Physiological Scholar. During his Presidency, the American Physiological Society formed its first Education Committee. He recounts in his article "Educational Activities In The Society" (*History Of The American Physiological Society, The Third Quarter Century*. edited by W. O. Fenn, Washington, DC: Am. Physiol. Soc., 1963, chap. 13) the stepwise evolution of the Society's educational activities since those beginnings. His concern, reflecting both his own development and his early experience in teaching undergraduate biology, was to provide advanced education for teachers, especially those in departments of biology in colleges. Workshops, summer fellowships, and acceptance for membership in the American Physiological Society became available to teachers of undergraduate physiology as a result of his initial efforts. "To my mind, the greatness of APS has consisted in its tradition of aspirations in research and teaching. Top satisfactions in my career came through the Society. I enjoy watching today's activities, maintaining and promoting the flexibility that makes the APS meaningful to its members," he wrote recently in *The Physiologist* [22(5):11, 1979].

Edward Adolph, who continues his active research today, insists that physiology is more than technology or information. It develops new aspects at every turn. As long as it lives, it will include unorthodox, which often becomes the standard of tomorrow. He warns, "Let not wisdom scoff at strange notions or isolated facts. Let them be explored. For the strange notion is a new vision and the isolated fact a new clay, possible foundations of tomorrow's science."

Melvin J. Fregly and Marilyn S. Fregly
University of Florida



The 26th Annual BOWDITCH LECTURE

New Computer Technologies and Their Potential for Expanded Vistas In Biomedicine

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The "computer age" presaged in the writings of science fiction since the 1930s has finally arrived. As was predicted many years ago, at least as great a proportion of the impact of computers has been on our private as upon our professional lives. Since the mid-1960s, the airline reservation system has been dependent upon online computer systems, as are now the planes themselves; computerized banking is now the rule rather than the exception in the United States, Western Europe, and Japan. The engine operations of Detroit-manufactured automobiles are or will soon be completely computer controlled; failure of the small processor responsible for ignition, timing, fuel flow, and fault identification may put the vehicle out of service. Few of us would attempt to balance a checkbook without a pocket calculator, a device which, though available for $20, possesses more computational power than the first giant computers built at a cost of millions of dollars slightly more than three decades ago. One of the world's largest manufacturers of slide rules ceased production a decade ago; almost incredibly, most electrical engineering students have never used or even seen a slide rule. The U.S. long-distance telephone network is not only run by computers but in actuality is nothing less than a giant network of communicating computers, which process and transmit the information content of human speech in the same manner by which they handle the burgeoning message traffic between yet other computers. Such examples have become so numerous and well advertised that even the most nontechnical of our population are now aware that these machines are inextricably linked with many critical functions of our society. Perhaps even more significantly, the realization is growing that the present pace of American life would be almost completely untenable without them; there is no longer any acceptable way to return to a world without the computers.

The professional lives of clinicians and biomedical scientists have been altered by the advent of the computer age. Many of us have come to rely on computer-driven word-processing machines, which allow one skilled secretary to perform the same tasks that would have required five conventional typists less than half a decade ago. A small "microcomputer" orchestrates the measurement functions of many modern biomedical research and diagnostic instruments, collating and printing results with a speed and convenience not even predicted less than a decade ago. Although the exploitation of computer technology by the biomedical sciences is not as advanced as in engineering, physics, and mathematics, a beginning has been made. The continuing synthesis of the capabilities of these two disparate disciplines is yielding a new armamentarium of tools and techniques that will assist in the exploration of the biological world.

This presentation discusses several of the elements of the new "biomedical computing" environment, both the biomedically motivated questions which require numerically based solutions and the emerging computational tools with which these questions can be investigated. Primary attention is given to several representative biomedical problems in which the computing requirements are of such enormous size or complexity that they rival the largest computational demands of that most well-known of all computer users, the military world. Biomedicine has not been traditionally recognized as a large consumer of computer power, in part because a number of the most interesting problems have until recently exceeded the state of the computer art. These difficult problems and their equally complex solutions are challenging areas of research, not only for the physiologists, biochemists, and molecular biologists but also for those of us who attempt to develop mathematical and computerized tools powerful enough to deal effectively with them.

Generation and Processing of Biomedically Relevant Imagery

The impact of computers on biomedicine has perhaps been best publicized in the discipline of X-ray computed tomography (CT). In the eight years since its introduc-

tion, the power of X-ray CT as a diagnostic tool has captivated our clinical colleagues. The long-espoused argument that computers do not create new knowledge but merely manipulate available information more rapidly than could the human has been placed in doubt by CT. The computerized generation of CT images cannot be replicated manually with paper and pencil in any practical period of time, if at all. The X-ray CT scaner melds an X-ray source and detector technology, which collects X-ray penetration data in a form useless to humans, with a computer, which by a complex mathematical process reorganizes the information content of these data to create an image of the body from an aspect not achievable with conventional radiographic equipment (7).

The developmental trends of these machines have been apparent since their introduction in 1973; enthusiasm for CT imagery has created a demand for ever-increasing spatial and gray-scale resolution, the ability to image ever thinner slices, and ever shorter durations between patient exposure and the final results. Although these enhanced capabilities are being achieved, an increasing burden is being placed on both the sophistication of the sensors and the computer technology. The magnitude of the increasing computer demand is of interest. The mathematical formulas, or "algorithms," which convert raw scanner data into the completed cross-sectional images, are extremely computation intensive; several thousand arithmetic operations (i.e., additions, subtractions, and multiplications) are required to produce, or "reconstruct," the gray-scale value of each small square element (called a picture element or pixel) in a computer-generated image. The minicomputers of 1973 executed approximately 200,000-500,000 arithmetic operations per second and could reconstruct an image of rather coarse resolution (80 × 80 pixels) within 5-6 min. By the late 1970s, however, both the resolution of the CT images (up to 512 × 512 pixels) and the speed with which they were produced had raised the required capabilities of the computers incorporated into the CT scanners to 10 million arthmetic instructions per second; several hundred million separate steps are now required to produce a typical X-ray CT image.

Barry K. Gilbert received the B.S. degree in electrical engineering from Purdue University, Lafayette, IN, in 1965 and the Ph.D. degree in physiology from the University of Minnesota, Minneapolis, in 1972, with minors in applied mathematics and electrical engineering. He is presently an Associate Professor of Physiology and Biophysics and a member of the Research Staff for the Departments of Physiology and Biophysics and of Diagnostic Radiology, Mayo Foundation and Mayo Medical School, Rochester, MN. His research interests include the design of special-purpose computers for highly efficient processing of biomedical imagery and the development of techniques for real-time processing of low-frequency biomedical signals such as aortic pressure and ECG data. Among his current research efforts are the design and development of computer hardware processing methods for an advanced X-ray computerized transaxial tomographic scanner, which will make possible near real-time three-dimensional image reconstruction of the dynamic anatomy of the lungs and beating heart of experimental animals and of patients.

These trends in CT scanner performance *1*) have propelled the state of the art of low- cost high-speed computing to its limits, *2*) have forced computer engineers to extend considerably the capabilities of modern small computers to satisfy the demands generated by this particular biomedical problem, and *3*) are continuing in several ongoing projects in computed tomography. As one example of such research in this field, it must be recognized that commercially available X-ray CT scanners are designed to record sufficient X-ray penetration data over a duration of a few seconds to reconstruct only a single cross section of tissue, 2-15 mm in thickness, during each scan (7). Commerical CT systems are thus incapable of providing clinical diagnostic or biomedical research data regarding the true anatomic shape of several important organ systems characterized by rapid motion. In X-ray computed tomography, at least three projects (6,20,28) are now underway to develop and test X-ray CT scanners which collect sufficient X-ray penetration data to allow the reconstruction of a set of images representing a stack of thin slabs of tissue of the organ of interest. One of these machines, the Dynamic Spatial Reconstructor (DSR), has the capability to image simultaneously up to 240 adjacent 1-mm-thick sections, and thereby every small volume of tissue throught an entire region of the body such as the thorax or abdomen.

The development of this machine, the DSR, has been underway in the Biodynamics Research Unit at the Mayo Clinic since 1971. The DSR is designed to scan over a span of 24 cm in the cephalocaudal dimension of the subject and can repeat the complete scan procedure at 16-ms intervals (i.e., at 60 repetitions/s) for durations of up to 20s. Reconstruction of this enormous mass of raw data allows the analysis of three-dimensional dynamic motion of the intact beating heart, breathing lungs, and other organs (28). Since the DSR is being used to investigate a variety of biomedical research and clinical diagnostic protocols, the system has been provided with a variety of scanning modes allowing imaging of both rapidly moving and stationary structures with a wide range of spatial, contrast, and temporal resolution. The nature of these capabilities may be observed in Fig. 1, which shows numerous cross sections reconstructed from the thorax and abdomen of a small monkey recently scanned in the DSR. Even a photomontage such as Fig. 1 cannot portray adequately the visual impact on the observer of a real-time three-dimensional radiographic image of the moving organs of the body.

Concomitant with this powerful set of imaging capabilities is an extraordinary demand on computational resources, generated by the need to reconstruct thousands of cross-section images (i.e., 240 cross sections/volume × 60 volumes/s) for each 1-s scan of the machine. For commercial scanners, arithmetic computation rates of 10 million instructions per second have been required to produce a single cross-section image in a few seconds. Quite similar equipment operating in support of the DSR at present requires several days to process only a small portion of the data generated in a single 10-s scan performed with this machine, a state of affairs that was predicted at the onset of the project in the early 1970s (12). To achieve processing times of a few minutes for a few seconds of data collection will re-

quire computation rates of 3 to 5 billion arithmetic operations per second, a rate that cannot be achieved in a cost-effective manner with 1981 computer technology. Achievement of a further reduction in processing times to produce nearly instantaneous results would require computation rates from 50 to 100 billion arithmetic operations per second, a capability that will not be available even at the state of the computer art until the latter half of this decade. As summarized in Table 1, these estimates of computational demand generated by the DSR exemplify a processing task originating from biomedicine far in excess of the capabilities of the current digital technology.

Ultrasound Imaging

A second mode of medical diagnostic imaging which has been widely investigated in the past few years relies on ultrasound as the probing energy. Ultrasonic transceivers operated in echo mode, e.g., in a manner analogous to submarine sonar, create images based on the backscatter of acoustic energy from reflecting substructures within the volume of tissue under study. However, it must be noted that these images are qualitative in nature, depending in large measure for their usefulness on the pecularities of each machine design and on the skill of the operator. It is apparently difficult even to compare images of the same individual made at different times by more than one technician (15).

The limitations of ultrasound echo scans have motivated investigations of more quantitative ultrasound imaging techniques relying on extensions of X-ray computed tomography. In X-ray computed tomography, the interaction between the impinging energy and the tissue through which it passes is limited to an absorption phenomenon that varies with beam energy. Ultrasound energy interacts with tissue in a more complex manner described by so-called wave equations, which predict the interaction of the tissue and the ultrasound waves. The tissue is assumed to be an inhomogeneous medium, possessing values of compressibility, density, attenuation, scattering cross section, and so on, which vary with location and orientation and with the center frequency and spectral content of the impinging energy source. Generalized wave equations written for such complex (i.e., typical) tissues cannot at present be evaluated in closed form with sufficient ease to allow the computation of the ultrasonic material properties for each element of tissue being imaged, as would be necessary to create a material property-dependent ultrasonic CT "image." Hence investigators have applied various simplifying assumptions and approximations to the general wave equations, thereby creating the basis of a transmission ultrasound CT imaging technique (15).

Because its physical structure is amenable to viewing from around 360°, the breast has been the organ principally investigated in transmission ultrasound CT studies. Ultrasound CT, though not exhibitng the spatial resolution of X-ray CT, nonetheless has provided quantitative images whose characteristics are independent of the equipment or the operator. Further, these images are in fact arrays of computer-generated numbers which are amenable to computerized enhancement and automated feature detection, itself a class of extremely powerful techniques (16).

Figure 2, a transmission ultrasound CT image of a breast, was generated in the laboratory of Dr. James Greenleaf at the Mayo Clinic and depicts several of the characteristics of ultrasound computed tomography. The various interaction modalities of ultrasound with

Table 1
Desired Level of Utilization of DSR—Dependence on Computer Power

	Engineering R & D; Limited Physiology	Practical "Off-Line" Application	Optimal "Off-Line" Application	Ultimate Real-Time Application
Time Period	1979-1982	1983-1985	1986-1988	Beyond 1988
"Desired" utility	Demonstrate technical feasibility	2-3 expt/day	CT fluoroscopy at least 8 expt/day	Real-time 3-D fluoroscopy
Compute load/expt	2,700 CS/expt (22.5 vol/expt)	16,200 CS/expt (135 vol/expt)	42,000 CS/expt (350 vol/expt)	
Compute load/day	2,700 CS	48,600 CS	336,000 CS	
Processing time/expt using commercial computers*†	3.75 h	22.5 h	2.4 days	
Processing time/expt-day using commercial computers*†	3.75	2.8 days	19.44 days	
Processing time/expt using Mayo-built computers‡	2.7 s	16.2 s	42 s	5-10 s; achievable in late 1980§
Processing time/expt-day using Mayo-built computers‡	2.7 s	48.6 s	6 min	50-100 s; achievable in late 1980s§

* Commercial computers: ModComp Classic, FPS AP 120B.
† Computation speeds with commercial computers: 10 min/vol.
‡ Computation speed with Mayo-built computers: 0.120 s/vol. (1 ms/cross section).
§ Computation speed with advanced Mayo-built computer: 0.030 s/vol. (250 μs/cross section).

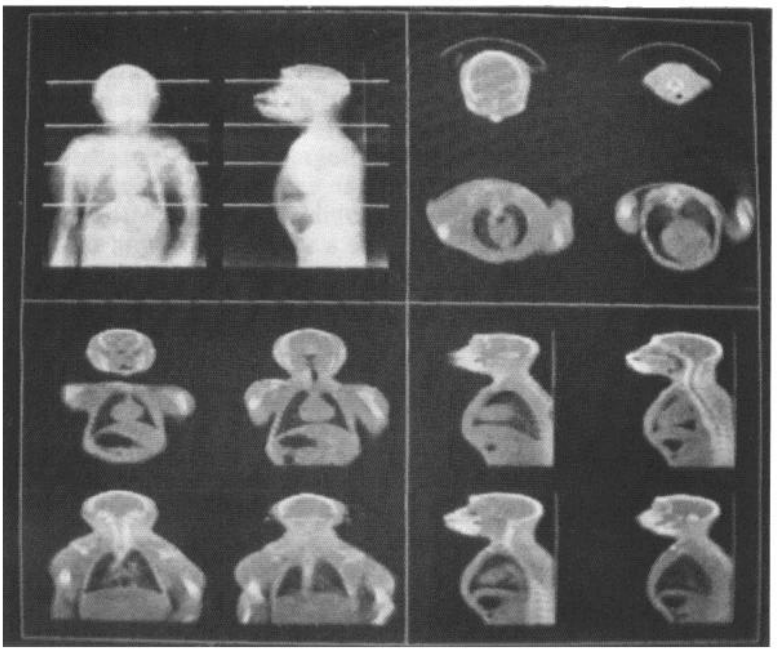


Figure 1
Results of scanning a small monkey in a true three-dimensional X-ray CT scanner, the DSR. Upper left images are conventional anteroposterior and lateral X-ray projections; horizontal lines indicate locations of transverse sections. After the entire volume of the head and thorax have been reconstructed, it is then possible to present, from the same data set, multiple transverse (upper right), coronal (lower left), and sagittal (lower right) section images of the head and thorax. [Reproduced with permission from R.A. Robb, X-ray computer tomography: an engineering synthesis of multi-scientific principles. *CRC Crit. Rev. Bioeng.* In press]

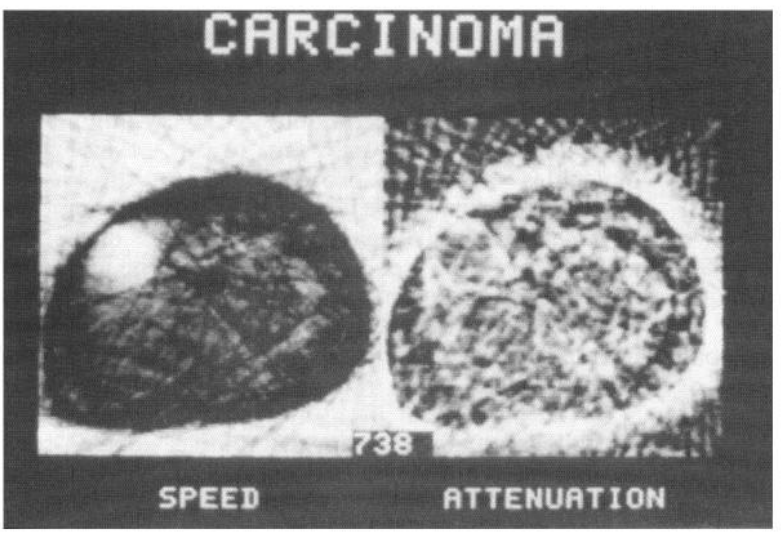


Figure 2
Complementary ultrasound CT images of in vivo human breast using two different types of interaction of ultrasound energy with tissue. Image reconstructed from measurement of speed of ultrasound in tissue clearly depicts in situ carcinoma; image reconstructed from attentuation measurements does not. [Reproduced with permission from Ref. 15]

tissue can all be exploited to create distinct sets of images related to the various material properties of tissue, such as attenuation and acoustic speed, which yield independent but supportive sets of results (14).

Ultrasound CT images of the type depicted in Fig. 2 have not yet attained the spatial and gray-scale resolution of X-ray CT images, nor are they as artifact free. The image blurring and artifacts result in part from instrumentation design limitations but in larger measure from reconstruction errors traceable to the above-described simplifications of the generalized wave equations, which render their numerical solution on a computer less time consuming and hence less costly. In principle, reliance on more accurate representations of the wave equations, which correctly account for the inhomogeneities in the tissue material properties, would result in reconstructed images exhibiting improved definition. The generalized wave equations are highly nonlinear but nonetheless appear to be soluble by "inverse-scattering" techniques, i.e., formal mathematical inversion procedures that require measurements of local instantaneous pressure around the object. At present, the high cost of implementing inverse-scattering methods on large computers has precluded aggressive attacks on these problems. The magnitude of the computational task for true three-dimensional ultrasound imaging through exploitation of the generalized wave equations in fact appears to be from one to several orders of magnitude greater than for the three-dimensional X-ray CT example described earlier (see Fig. 4).

Another limitation of ultrasound CT has been the requirement for a scan of 360° around the structure of interest. However, it may be feasible to generate true ultrasound CT images, not in transmission mode as displayed in Fig. 2, but from backscattered energy; an ultrasound CT device exploiting backscatter would thus function in echo mode but would generate a truly quantitative reconstructed image (8).

Biomedical Image Processing: Digital Radiography

Diagnostic radiology is experiencing its second major technological development in less than ten years (the first was the introduction of X-ray CT in 1973). In this new technique, called digital radiography or digital

fluorography, a conventional X-ray tube and fluorescent screen-image intensifier are employed in the recording and display of standard angiograms; however, since the consecutive dynamic images are recorded in video rather than film format, they can thereafter be converted into digital representations that can be processed directly by a computer. At present, numerous advantages have been described for this new method of treating otherwise conventional angiographic imagery, not a few of which are clearly overstated. The contrast range of a conventional film-screen combination is from 500:1 to 1,000:1; current-technology fluorescent screen-image intensifier-video camera combinations are incapable of exhibiting higher contrast ranges, if as high. Unfortunately, the maximum spatial resolution of digital radiography is currently about 1 line pair/mm, whereas film can resolve 3 low contrast line pairs/mm and 8 high contrast line pairs/mm. The spatial resolution of digital radiography is a design constraint of the present image intensifier-video camera combinations; though several commercial units have been announced or are in development, all will have to contend with the problem of image spatial resolution until more advanced intensifiers and cameras now in laboratory development become commercially available.

The compelling advantage of digital radiography, however, is that the images can be processed by a digital computer to improve global or local contrast or to enhance the edges of substructural features in the image, most frequently by a pair of techniques jointly known as subtraction radiography (26). In the first of these methods, a sequence of image frames is recorded during a given portion of the cardiac cycle both before and after the injection of radiopaque contrast medium. Computer-converted image frames from the two sequences are paired and then subtracted from one another on a pixel-by-pixel basis. If the members of each pair of images are identical except for the presence of radiopaque dye in one of them, subtraction will reveal the presence of the bolus of dye. This technique, which in effect markedly enhances the apparent contrast of the iodine-containing dye, also improves the visibility of the cardiac chambers and vasculature of any organs that contain the dye at the instant of the recording. The technique is not efficacious for all organs; for example, several investigators have reported only moderate success in the visualization of the cerebral vasculature (26).

In the second approach to digital radiography, as the contrast injection is performed, successive images recorded at a 60/s rate are exposed with the X-ray tube operating alternately at two energy levels, e.g., 60 and 120 kVp. Since the higher energy level X-ray beam exhibits greater penetration than does the lower energy beam, particularly through the iodine-containing contrast agent, sequential pairs of images can be subtracted from one another to reveal the presence of the radiopaque dye. This approach removes structural superposition mismatches to a greater extent than does the temporal subtraction technique discussed earlier but does not enhance the apparent gray-scale contrast of the dye as well as does the temporal subtraction method.

Because digital radiography is currently at an early stage of development, many unresolved questions regarding its strengths and efficacies and its weaknesses remain to be investigated. Some, though not all, of its limitations may be related to current machine design for which technological improvements can be identified; however, the problem of superposition failure is a constraint which is not susceptible to improvement through changes in scanner design. Conversely, the obvious strengths of digital radiographic may not easily be equaled by conventional radiographic methods; the potentially powerful capability to interact with these images by computer will be a strong motivating force for continuing evolution of this new diagnostic imaging modality.

Molecular Modeling, Drug Design, and Biochemical Reaction Kinetics

The capabilities of powerful digital computers and computer-driven real-time color displays are beginning to alter the tools and methodology of biochemical research. With the aid of specialized computer hardware and software, it is becoming feasible to study the detailed structure of complex macromolecules and their active binding sites and to investigate the interactions of receptors and the pharmacophoric sites on active drugs, as well as the reaction kinetics of these molecular interactions.

Formerly, most of the methods employed to study these facets of macromolecular structure and function could only indirectly probe the molecules under investigation, and in general, only X-ray crystallography could delineate the atomic substructure of biological molecules such as proteins. From the X-ray crystallographic data the investigator was then compelled to build laboriously a physical three-dimensional stick-and-wire or "CPK" space-filling model of the molecule. Such models are often so fragile or so complex in appearance that it is possible only to stare at them. Active intervention, the ability to ask "what-if" questions, is difficult at best.

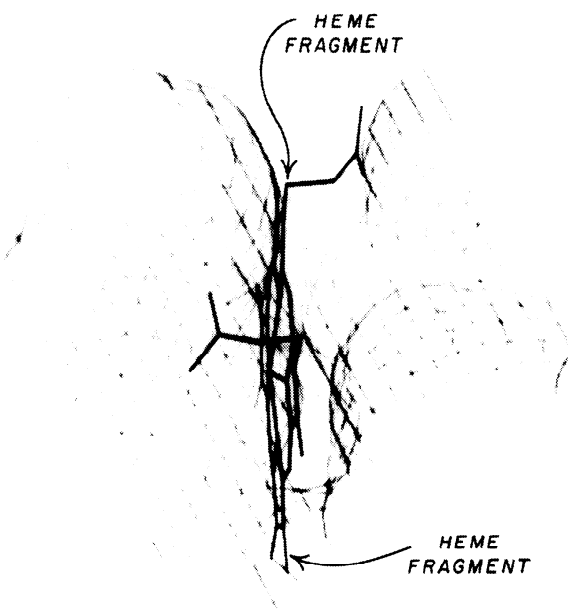
It is now feasible, however, to enter the crystallography data for any macromolecule, e.g., for a protein receptor structure (if such is known) and several candidate pharmacophores into a computer, then to display the molecules in color, and via rotation of the image, to create progressively a three-dimensional representation of the structures or any part thereof from any desired angle of view (22). Appropriate computer programs allow one to "peel away" the outer portions of a complex molecule to reveal its inner structure, which may contain important voids or invaginations, and even to present a view of the molecule from its inside looking out. The volume-filling structure of the molecule can then be calculated from an estmate of the three-dimensional conformation of its electron charge cloud. Thereafter, by rolling a test ball whose radius is that of a water molecule over the surface of the macromolecule under investigation, an improved understanding of the potentially important invaginations and pockets which may be the physical locations of receptor sites may be obtained.

It has been pointed out that because macromolecules are flexible and can distort in one another's presence, sole reliance on crystallography data to assess possible active sites on these structures may be misleading. Hence computer programs have been developed to identify single covalent bonds in the vicinity of a potential receptor site or pharmacophoric structure and to rotate,

stretch, and bend these bonds while comparing the resulting three-dimensional conformations of the receptor site and the potential pharmacophore (25). In addition, these flexion-torsion studies may be combined with calculations of the total bond energy in the structure that includes the active site to assess simultaneously the "most probable" shapes of receptors and potential pharmacophores in the presence of one another (29). In addition, specialized computer programs can substitute one substructural fragment for another in the potential pharmacophore; using a computer-controlled color graphics screen, the investigator can identify a small subsection of the entire complex molecule, interactively replace, for example, an existing structural moiety with another fragment of somewhat different three-dimensional conformation, and retest the pharmacophore for activity. Although the results of these computer simulations are occasionally incorrect and should always be verified by experiment, this computer-based approach not only allows a very rapid and thorough analysis of existing structures but in a very real sense allows true computer-assisted design of drugs.

The computer power of presently available drug design systems, which rely on a large minicomputer and sometimes on an associated special-purpose arithmetic unit or "number cruncher" called an array processor, limits the exhaustiveness of computer searches of potentially matching pharmacophore-receptor conformations to the rotation and bending of not more than four interatomic bonds, whereas it has been pointed out that the ability to test 8–10 bonds or occasionally even more, would be a powerful extension of present capabilities (25). The 4-bond problem requires about 10-12 million arithmetic operations per second, whereas the 10-bond problem may require 40-50 million arithmetic operations per second.

Figure 3



Computer-generated image of that portion of myoglobin molecule containing oxygen-carrying heme fragment. Note that heme is tightly bound within invagination of myoglobin protein structure. [photo courtesy of Franklyn Prendergast, Mayo Foundation, and C. David Barry, Washington University]

The power of the computer-based molecular modeling techniques is exemplified by recent investigations by Dr. Frank Prendergast of Mayo Foundation (in collaboration with Dr. C. David Barry of Washington University) of the structure of myoglobin, the fluorescence of apomyoglobin and apomyoglobin fluorophore complexes, and particularly the interactions between myoglobin and apomyoglobin. By removing the heme fragment from the myoglobin by chemical means and then interacting the resulting apomyoglobin with various fluorescent probes including a fluorescent porphyrin, protoporphyrin X, Frank and David have been able to demonstrate that the heme is a planar structure trapped within a chasm-shaped cavity of a peculiar three-dimensional conformation (Fig. 3). This "pocket," which is structurally rigid, is just sufficiently larger than the planar heme fragment to allow oxygen molecules to creep into the cavity and bind to the heme. In addition, it appears that oxygen can also dissolve in a secondary hydrophobic pocket in the protein distal to the heme ring. By means of computer-based molecular modeling studies exemplified by Fig. 3, Frank and David have not only elucidated the conformation of the heme and its surrounding pocket but have also identified two tryptophan residues in the myoglobin molecule which can transfer energy nonradiatively to a heme moiety or to any of a number of fluorophores bound in the heme pocket. Most importantly, by examination of the relative orientations of these tryptophans and upon consideration of the physical principles that govern transfer of energy by nonradiative means, it has been possible to deduce that tryptophan 14, which has its ring coplanar with planar molecules in the heme pocket, is the major contributor of energy. These structural data obtained from the computer modeling corroborate data gathered by spectroscopic techniques, the latter of necessity being able to provide structural information only indirectly. Finally, the computer modeling of apomyoglobin has shown that both tryptophan residues and flouorophores in the binding pocket are structurally constrained, so much so that they cannot "rotate" independently of the motion of the whole protein molecule. Again, these findings corroborate spectroscopic data suggesting that the two tryptophans and the fluorophores bound in the heme pocket were immobile on a nanosecond time scale.

These results are improving the understanding of the entire mechanism by which heme and oxygen bind to one another, the role played by the protein structure of the myoglobin in this complex biochemical reaction, and, moreover, the factors that influence intramolecular fluctuations in protein structure. The entire set of capabilities for computer analysis of macromolecules and synthesis of drugs thus promises significant advances in the state of the art of quantitative pharmacology and will be further enhanced by advances, to be described below, in the computer technology that supports this biomedical research discipline.

Additional Computer-Supported Biomedical Disciplines

The three examples presented above of the application of computer-based methods and techniques to biomedicine are by no means unique. Computerized analysis of electrocardiograms and computerized pa-

tient monitoring are additional examples. Although debate continues regarding the benefits of on-line patient monitoring, it is less heated than formerly and appears to be a trend in favor of the computerized approach. Automated analysis of the electrocardiogram (ECG) is now routinely employed in some large medical centers and, with the aid of remote telephone transmission of ECG data, in many smaller facilities as well; the efficacy of this technique was also debated during the past decade, but again the computerized approach is becoming accepted.

Finally, there is continuing interest in the use of computers to evaluate mathematical models of biological processes, including the transport of gases and nutrients across biological membranes and the electrical conduction properties of nerve and muscle fibers as a function of local concentrations of ions in the bathing medium (4). Computerized analyses of the fluid mechanics of blood flow through the vasculature and particularly through the cardiac chambers and around prosthetic heart valves have been performed for the past decade by several investigators (5, 10, 13). The stress and strain patterns in the walls of the cardiac chambers have also been investigated using techniques originally developed to quantitate these forces in complex man-made structures such as airplane wings (27). Many of these applications, especially the modeling and blood flow problems, are of such large computational magnitude that they can easily consume the most powerful computational resources currently available or envisioned for the near future.

In summary of the above comments, several interesting and potentially useful biomedical research and clinical diagnostic projects currently under way are employing or even stressing the state of the computer art, particularly if cost-effectiveness must also be considered. Perhaps of even greater significance, in many cases the biomedical problems have compelled and biomedical researchers have actively sought computerized solutions and technology, and not vice versa. As will be described in the following sections, all aspects of the computer technology are rising to meet these challenges.

Advances in Computer Technology

Many observers of the science of digital computation commonly assume that the capabilities of each successive generation of computers are reflections of the state of the art of every aspect of digital technology at that instant. Such implications are misleading, however, since 5–10 years must usually elapse before the newest generations of integrated circuits appear in commercial computers. The computers recognized as current state of the art, whether large minicomputers or mainframe computers, have all been available since the mid-to-late 1970s and were developed in the early-to-mid 1970s, using components designed in the late 1960s and early 1970s; microprocessors display a somewhat shorter gestation duration of 3–5 years. It is probable, however, that the technology currently on the drawing boards and now emerging from electronics research laboratories will improve the performance of the computers of the mid-to-late 1980s by a performance/cost factor of 100-1,000. Several of the numerous areas in which difficult biomedical problems may be attacked in the future will be reviewed.

The Struggle with Software

The interaction between humans and computers relies on several hierarchical layers of "computer languages." The lowest of these, that of the computer itself, is called machine language, or assembly language; although computer programs can be and are prepared in such a language, an intimate knowledge of the detailed operation of each given machine is required. No two computer designs are identical or use the same machine language, and each design becomes obsolescent within 3–5 years as ever more capable computer architectures are developed by the manufacturers (e.g., there have been four distinct generations of microprocessors since 1970). It is thus almost impossible for all but the most dedicated software specialists to master the fundamental language of each new computer.

As a result of the confusion generated by frequent changes in computer machine languages, a series of so-called "higher level" or "higher order" languages began to dominate computer programming more than 20 years ago. The first of these, a language similar to algebra, developed under US Department of Defense sponsorship and referred to as Formula Translation, or FORTRAN, attempted to insulate the programmer from the underlying details of machine structure. This new software development approach was intended to improve the portability of programs among computers regardless of their internal designs. The results of this experiment have been mixed; although it was no longer necessary for programmers to comprehend the details of each machine design, numerous syntactic limitations of the early FORTRAN versions soon became apparent, resulting in the uncontrolled proliferation of special extensions of that language, each with unique features and capabilities. There are at present so many slightly different FORTRAN language forms that it is difficult to transfer a computer program between machines of different manufacturers and even between diffferent models of computers manufactured by a single company.

FORTRAN and several similar languages such as BASIC soon exhibited an additional problem to which strenuous research effect have recently been addressed. FORTRAN is frequently referred to as a "bottom-up" higher level language; ie., the structure of the language is such that the programmer must commit a very large proportion of his effort to the details of each section of the program at the expense of the broad conceptual aspects of the problem; fundamental logical constructs of a given program are often obscured by its detail. In addition, several linguistic features of FORTRAN and BASIC inadvertently encourage the preparation of programs that are difficult to understand, correct, or expand; it frequently becomes necessary to discard and rewrite a large program because its documentation does not allow minor corrections or enhancements to be installed with ease.

To make matters worse, by the late 1960s several disturbing conclusions began to emerge from numerous studies of the productivity of hardware and software designers. These reviews demonstrated that the productivity of hardware designers and the performance of integrated circuit devices had been roughly doubling every 3 years since 1960; conversely, during the same 10-year duration, the productivity of software

Table 2
Comparison of Two High-Level Computer Languages

FORTRAN Example

```
      INTEGER FUNCTION FACTRL (NUMB)
      INTEGER NUMB, ISUBTL, INC
      FACTRL = 0
      IF (NUMB.LT.O) GO TO 300
      ISUBTL = 1
      IF (NUMB.EQ.0) GO TO 200
      DO 100 INC. = 1, NUMB
        ISUBTL = ISUBTL * INC
100   CONTINUE
200   FACTRL = ISUBTL
      RETURN
300   WRITE (6, 400) NUMB
400   FORMAT (1X, 'ERROR NEGATIVE NUMBER', I10,
     *  'PASSED TO FACTORIAL FUNCTION')
      RETURN
      END
```

Summary

16 Lines of code
3 Variables
2 Termination points
"Go to" (spaghetti) logic
Recursion not supported
Line oriented statements

Pascal Example

```
FUNCTION FACTORIAL (NUMB: INTEGER): INTEGER;
BEGIN
 FACTORIAL : = 0;
 IF (NUMB > = 0) THEN
  CASE NUMB OF
   0: FACTORIAL : = 1 ;
   OTHERWISE
    FACTORIAL : =NUMB * FACTORIAL (NUMB-1)
  END
 ELSE
  WRITELN ('NEGATIVE NUMBER', NUMB,
    'PASSED TO FACTORIAL FUNCTION')
END
```

Summary

13 Lines of code
1 Variable
1 Termination point
Block structured logic
Recursion supported
Statements separated by semicolon ;
Easy to read—most important feature

developers barely increased by 50%. More recent studies conducted during the late 1970s have corroborated those early findings. Stated alternately, software written in the late 1970s was prepared at roughly twice the pace of equivalent software written in primitive versions of the same languages in the early 1960s, whereas hardware productivity has increased by roughly a factor of 100–1,000 since 1960. This tremendous disparity in productivity advances between hardware and software has led to the inescapable conclusion that in the 1980s hardware will be virtually free of charge, while the cost of software will dominate all computer projects both in cost and in elapsed time to completion. In short, computer hardware has become 1,000 times more powerful in the past two decades, while the ease with which we can communicate with these machines has barely improved at all.

As a result of these trends, already apparent more than a decade ago, strenuous attacks on the productivity problems associated with high level FORTRAN-like languages were initiated in the late 1960s. As a result of these development efforts, an entirely new family of languages, referred to as "structured" or "top-down" languages, has arisen. The new languages permit the expenditure of balanced efforts on the overall structure of a program and on its details. The sequence of instructions in a structured language program appear in a hierarchical fashion that is quite apparent when reviewed by someone other than the preparer. For example, in a section of computer "code" written in a structured language, the very first statements establish the major constraints of the task to be performed; successive instructions refine this task definition in ever greater detail, with the final statements delineating the finest granularity of detail. Programs prepared in a structured language thus appear similar to an outline; in many cases, the computer printer even indents the statements for ease of reading. In addition, the statement syntax is "conversational," using such words as WHILE, THEN, IF, ELSE, FOR, and so on.

The first attempt to create such a structured top-down language was a European effort. Observing the unfortunate experiences of the Americans, the European scientific community never completely adopted FORTRAN. Western Europe served as a development and testing ground for the strengths and deficiencies of several generations of structured languages and concepts. One of these languages, referred to as Pascal (after Blaise Pascal), is finding wide acceptance in Europe and the United States (18). Table 2 depicts a section of FORTRAN in a side-by-side comparison with an equivalent section of Pascal as well as a summary of the salient features of both sections of code.

Lastly, a very advanced top-down language, a super-Pascal, developed with Department of Defense sponsorship, will be introduced in approximately 2 years. This new language, under development in Western Europe and the United States since 1975, is called Ada.[1] Ada is a very powerful and comprehensive though a very complex language; there is considerable debate regarding the probability that it will supplant the earlier structured languages, particularly Pascal (1). The structured languages are already in use in the engineering disciplines and are beginning to appear in some scientific programs prepared for biomedical research purposes, though their application to clinical tasks is somewhat less likely.

In contradistinction to the scientific languages described above, so-called conversational computer languages will become widely available as individuals without formal computer training are increasingly compelled to communicate with these machines. An example of such a language, called Query By Example, or

[1]Ada Augusta, Countess of Lovelace, daughter of George Gordon, Lord Byron; Lady Lovelace, in effect the world's first computer programmer, collaborated with Charles Babbage in the 1840s to develop the earliest known mechanical device which was truly a digital computer.

QBE, allows conversational sentences and phrases to be employed in all communications with a computer (30). At present these languages place enormous computational burdens on the computers that support them, since considerable machine translation effort is necessary to convert the conversational phrases into executable machine language instructions. However, in some cases, the large markets, primarily in the business world, exposed by the conversational languages render the additional load on the computer's cost-effectiveness. As these machines become more capable, the overhead required for the language conversion will decrease, thereby considerably widening the access digital computers for the general populace. Although these developments will not immediately affect the biomedical community, it is probable that they will insinuate themselves into the clinical and perhaps the research environments over a duration of years.

Improvements in Hardware

Although improvements in software will certainly render the coming generations of computers "friendlier" to the user, the major advances are occurring at the device physics level; quantum-jump improvements in the technology of integrated circuit fabrication will, by the end of this decade, result in a massive increase in performance levels and cost-effectiveness of computers, access to which will be widely available. The state of the electronic computer art has in fact traversed several generations of technology, begun by the British and Americans in 1943 and continuing to the present. The first generation of machines used several tens of thousands of glass vacuum tubes as the switching elements. By the late 1950s, the advent of the germanium transistor had led to the first generation of completely "solid-state" computers, including early offerings by IBM, Univac, and Control Data. In the early 1960s, the third generation of computers began to employ the first primitive silicon integrated circuits. The performance of these silicon integrated circuits has improved so markedly during the past 20 years that all commercial and military computers exploit one form or another of silicon device technology, as will be predominantly the case for the next 10-20 years. These developments, though somewhat esoteric, are so fundamental to an understanding of the coming advances in computer capabilities that several examples of this burgeoning technology will be discussed.

Definition of Terminology

First, several terms must be defined. A gate is a minimum reducible element of digital computer logic. For example, a two-input AND-gate is a logical structure that examines two input signals, and if both input signals are logically "true," then and only then will the output of the gate also become true. If either of the inputs becomes "false," the output of the gate immediately becomes false as well. Conversely, a two-input OR-gate is a device whose output become true if the logical states of either or both of its two inputs is true; only if both inputs become false does the output also become false. Although these two functions, plus a handful of others, are conceptually straightforward, they represent the basic computer operations from which all other logical and arithmetic functions are constructed.

The second term to be introduced is that of "system clock rate." Almost all digital computers designed during the last decade have relied on the "ticks" of an internal crystal-controlled "clock" to orchestrate their step-by-step operation; the ticks of the clock are converted into a series of digital pulses separated by uniform time intervals that propagate throughout the machine and enable the execution of the individual machine steps. In general, the higher that rate, or " frequency," of the system clock, the faster the computer operates, the more work it can perform, and the more sophisticated is its technology. Conventional microprocessors currently employed in a variety of cash registers, gas chromatographs, mass spectrographs, etc., usually operate in the range of 2-5 million clock ticks per second, or 2-5 MHz. The world's most powerful computers (referred to as "mainframes") employ clocks with frequencies of 50-80 MHz, clearly a state of the art development when it is recognized that at 80 MHz, the spacing of the clock pulses in their traversal of the wiring inside the computer (at 0.7 times the speed of light) is approximately 10 ft. Some experimental systems, several of which have been fabricated in our laboratories at Mayo Foundation, have employed clock frequencies as high as 0.5 billion cyles per second, or 0.5 GHz, in which the pulse-to-pulse spacing intervals of the clock signal in the machine wiring are less than 2 ft.

Performance and Complexity Measures of Digital Computers and Selected Computational Tasks

The two major advances of integrated circuit technology during the past two decades have been *1*) an increase in the clock rate at which integrated circuits and entire computer systems can be operated and *2*) the inclusion of ever greater numbers of gates on single "chips" of silicon approximately 0.125-0.25 in^2. These two values, i.e., the number of gates on a chip, or in an entire computer system, and the speed at which the system can operate, have been combined into a measure of the complexity of a computational task as well as the capability of any given computer to execute that task. This performance measure is, simply stated, the "gate-Hertz product." When this criterion is applied to the performance of a single integrated circuit of given dimensions, the performance measure is modified slightly to account for the silicon area required to contain all the gates and is then stated as (gate • Hz)/cm^2.

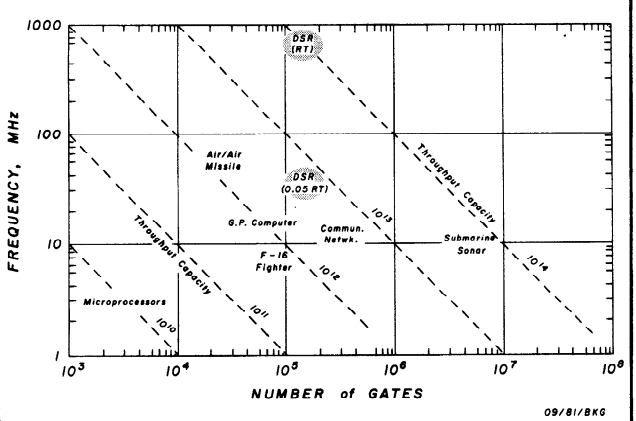
Another widely employed performance measure, closely related to the gate • Hertz product described above, is the time required for a logic gate to decide on the state of its output after it has been presented with a change of logical values on its inputs. This measure, the "gate propagation delay" stated in nanoseconds, is related to the sophistication of the particular silicon device fabrication technology to a much greater extent than it is to the design of any given gate. The shorter the typical gate propagation delay, the faster the components of a particular logic family are capable of making decisions, and the more work can be accomplished by a typical integrated circuit within 1s.

To provide a sense of perspective of the number of basic gates required to perform a familiar arithmetic

operation, consider the multiplication of two relatively low precision integers spanning the range from 0 to 255 (in computer parlance, this would be the multiplication of a pair of 8-bit numbers, since 8 binary bits can represent any value from 0 to 255). The computer hardware that performs this task must contain 1,008 gates connected to one another in a parallelogram-shaped array. If we want to multiply larger integers (e.g., containing 32 binary bits) that can represent any value from 0 to 4.3 billion, a multiplier for this task contains approximately 16,240 gates.

With these concepts in mind, it may now be instructive to compare the computational complexities of several large processing tasks, some borrowed from the military and some from the world of biomedicine, using the gate • Hertz complexity measure. Because of their absolute requirement for instantaneous processing of vast quantities of data in life-and-death battlefield environments, it has been assumed that the largest known computational tasks would always be generated by military requirements. Figure 4 plots the operating frequency of and the number of gates required by the computers which must execute these tasks. The diagonal dotted lines represent performance products from 10^{11} to 10^{14} gate • Hz, covering a range of computation rates from one million to fifty billion arithmetic operations per second. The processing rates for the DSR, which are presented at two levels, 0.05 of maximum data utilization and maximum data utilization, compare favorably in magnitude to the most complex military computational problems known today. Though not included in Fig. 4, preliminary estimates of other biomedical computational tasks, such as molecular modeling and real-time ultrasound CT, indicate that they are at least as large as the 0.05 data utilization DSR problem and may be even larger. These comparisons indicate clearly that massive advances in processing technology will be required to solve many of the most interesting biomedical problems.

Figure 4



Comparison of the processing complexity of selected biomedical [e.g., DSR (RT) and DSR (0.05 RT)] and military computational tasks. Ordinate and abscissa represent required raw computer speed and number of computer elements (gates), respectively, to perform any given task. Diagonal lines are products of the ordinate and abscissa values, which represent "constant-complexity" loci. Biomedical tasks can be as large as or larger than military tasks; until recently it has been assumed, erroneously, that the largest computational tasks would always arise from military requirements and not from any other source (see text).

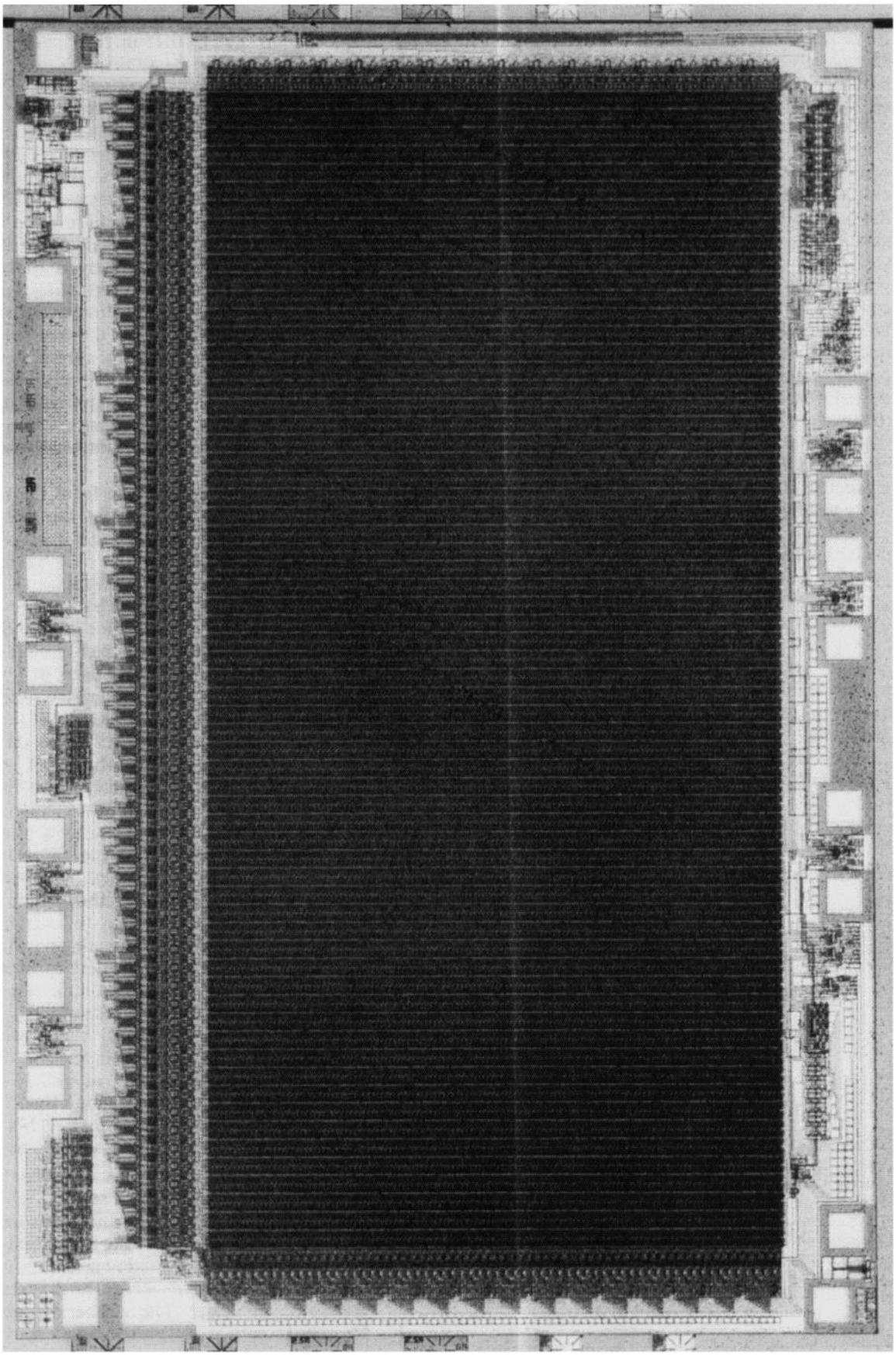
Advances in Integrated Circuit Technology

The fabrication technology of silicon integrated circuits has undergone revolutionary advances since the early 1960s. Beginning with an ability to construct a half dozen gates on an integrated circuit in 1960, it is now becoming feasible to fabricate a component containing 20,000-25,000 gates on a single chip of silicon of approximately 0.15 by 0.25 in. (see Fig. 5). Increases in integration levels can be attained by increasing the size of the silicon chip or by decreasing the geometric size of and spacing between the individual gates on the chip. For practical reasons involving the difficulty of building physically large integrated circuits, the only viable option for the manufacturers is the fabrication of ever-smaller structures on each integrated circuit. The dimensions of these structures, including the individual transistors and their interconnecting aluminum conductors, are usually measured in microns (μm). In 1960, the dimensions of the smallest structures laid down on the silicon surfaces by photolithographic techniques were approximately 30 μm. These dimensions have decreased by a factor of two every 6 years from the early 1960s until 1980; the geometries of the most advanced devices now in production are now approximately 2.0 μm (3), while integrated circuits fabricated under laboratory conditions have used minimum device dimensions of 0.2 μm (2,000 Å).

Several advantages accrue from these improvements in fabrication technology. As the dimensions of the smallest integrated circuit structures decrease by a factor of two, for example, their packing density on the integrated circuit increases by a factor of four, the speed of the entire circuit increases by a factor of two, and the power dissipation of the device (the amount of power it takes to operate the integrated circuit) decreases by a factor of four. Hence, to the users of the integrated circuits, shrinkage of device geometry yields many advantages and very few disadvantages (3).

The converse is true, however, for the vendors of the integrated circuits, since problems of manufacturability, the percentage of correctly operating components, and their susceptibility to electrical interference and radiation damage, all increase by a power function of the dimensional shrinkage factor. Consider some of the problems facing the "chip" designers. An integrated circuit is fabricated by a photolithographic technique quite similar to magazine-quality four-color photographic printing; a thin wafer of pure silicon is first oxidized in a high oxygen content atmosphere to produce a layer of silicon dioxide on top of the bulk silicon. The silicon dioxide, a good electrical insulator, is in turn coated with a chemical photoresist, which when exposed to light is altered in chemical composition. The areas of the photoresist exposed to light, as well as underlying portions of the silicon dioxide, may then be dissolved by other chemicals, while those regions not so exposed are unaffected by the solvents. A pattern may be impressed on the photoresist and on the oxide coating through an optical mask, followed by a series of chemical etching, reoxidation, and remasking and exposure steps, until, as is clearly visible in Fig. 6, the individual features of the integrated circuit are laid down one above the other in a "Dagwood sandwich" structure to create the desired transistors and gates. The number of such steps required to manufacture an integrated circuit is never less than 10

Figure 5
Photomicrograph of a state of the art, 16,000-bit computer memory component. Silicon ship has dimensions 0.13 × 0.25 in. and contains 20,000 gates. Minimum feature size is 2 μm. [Photo courtesy of Fairchild Camera and Instrument]



and may be as many as 30; masking and etching resolution in the lateral direction and between the different layers is absolutely crucial, since registration errors between adjacent layers result in a malfunctioning component.

As implied earlier, the operating speeds of individual components are also rising dramatically. The use of integrated ciruits operating at higher speeds allows higher clock rates for the entire computer, which in turn leads to higher arithmetic computational rates, usually by exactly the factor of the clock speed increase. Increases in computer speed have already played a considerable role in the design of the largest commerial computer, which, along with many military applications, have always been in the vanguard of machines demonstrating increased performance. Over the last 15 years, the gate propagation delays (i.e., the reciprocal of gate "speed") of successive generations of silicon devices have decreased steadily from a range of approximately 30 ns for conventional devices in the early and mid 1960s to less than 200 ps for the newest state of the art integrated circuits. A half-dozen high-technology computer manufacturers and research facilities, including our own laboratory at Mayo Foundation, are now exploiting these new high-speed components in a variety of advanced computer designs. Several large general-purpose machines have now been developed whose system clock rates exceed 80 MHz and execute arithmetic at rates up to 400 million arithmetic operations (i.e., additions, subtractions, and multiplications) per second (24); special-purpose image processing computers developed in our laboratories at Mayo Foundation operate at 100-500 MHz speeds, and perform computation at rates of 1.8 billion arithmetic operations per second. These devices are capable of performing 10–30 times as much computation each second as would equivalent computers employing less advanced integrated circuits with a similar number of components.

As described earlier, there have been several generations of computational device technology, beginning in the early 1940s and continuing to the present, with highly complex silicon integrated circuits. There is now a harbinger of a fourth generation of integrated circuits, based not on silicon but new substrate materials whose device physics properties result in improved electrical characteristics as well. These new materials are usually crystalline salts of Group III and V metals and nonmetals in the Periodic Table, the two most promising of which are gallium arsenide and indium phosphide. Unfortunately, the III-V crystals have proven to be extremely resistant to the conventional integrated circuit fabrication techniques that work very well for silicon. However, they are attractive for the manufacture of such devices because the mobility of

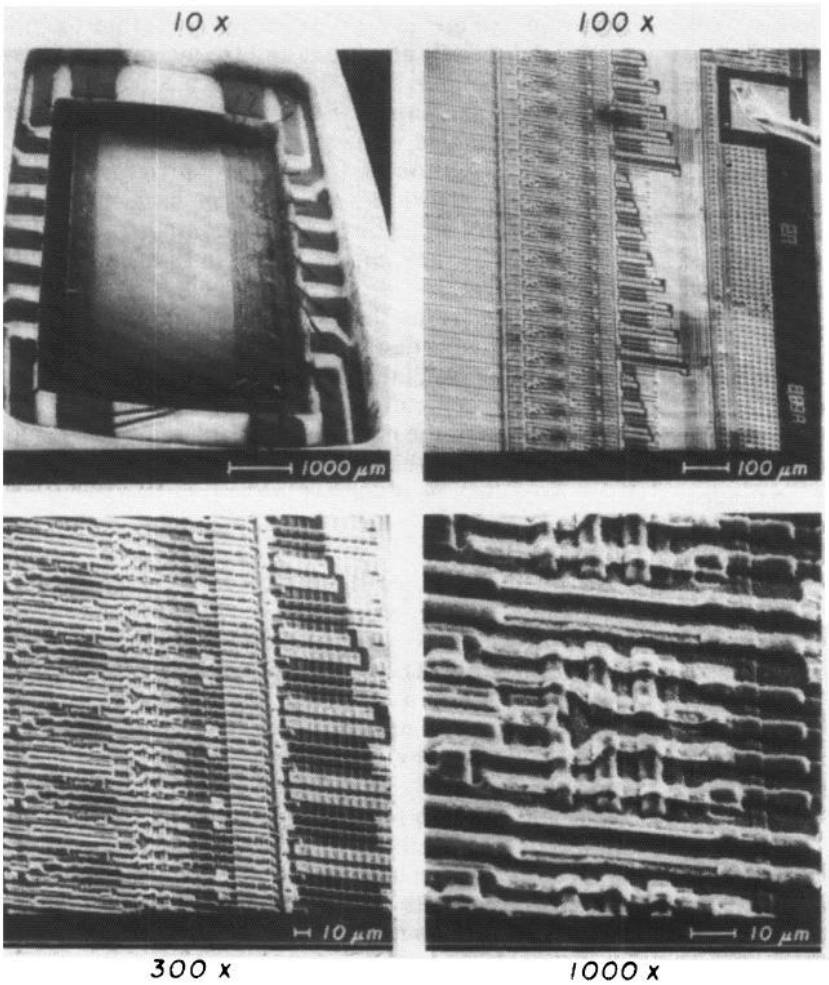
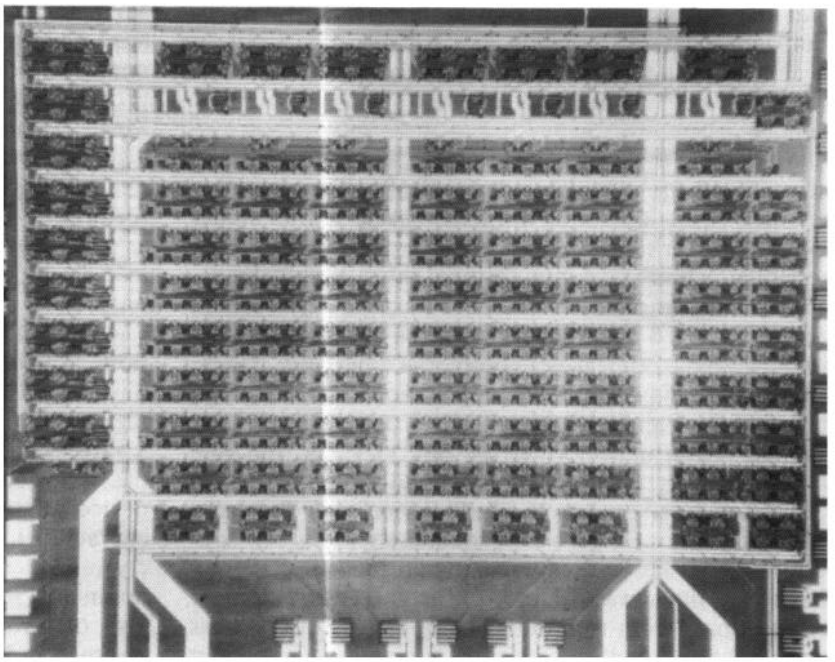


Figure 6

Scanning electron micrograph of state of the art, digital memory component of Fig. 5 at several magnification levels. Note "Dagwood sandwich" appearance of the surface structures. *Minimum* feature size is 2 µm. [Component courtesy of Fairchild Camera and Instrument]

Figure 7
An experimental arithmetic "chip" of dimensions 2.2 × 2.7 mm manufactured from gallium arsenide. This component multiplies two integer values in 6 ns, i.e., roughly 10 times faster than possible with conventional silicon technology. [Photo courtesy of Rockwell International]



free electrons in bulk gallium arsenide and indium phosphide is five or more times greater than the electron mobility in the equivalent silicon material (9). In a manner analogous to the case of two membranes with low and high permeability to a given ionic species, the gallium arsenide crystal allows more electrons to traverse its structure per unit time for a given voltage gradient; as a result, gates fabricated with gallium arsenide demonstrate higher performance than those fabricated with silicon. The resulting improvements in performance, which can be exploited in a variety of ways, e.g., increased gate speed for the same gate power requirement, decreased power levels for the same gate speed, or increased packing density with a combination of speed and power enhancements, are all well worth achieving in practical circuits (Fig. 7). However, the need to achieve improved fabrication technologies for gallium arsenide integrated circuits will probably limit the exploitation of these components until the end of this decade.

The potential benefit to biomedicine of continued developments in gallium arsenide and other semiconductor compounds is particularly intriguing, because in theory the fabrication of extremely high-density integrated circuits, including powerful microminiaturized computers called microprocessors, should be possible; these would require extremely low operating currents and low supply voltages and would dissipate one to two orders of magnitude less heat than the lowest power silicon circuits. As an example of the utility of such a technology, an implantable cardiac pacemaker could incoporate an "on-board" computer capable of monitoring the function of the pacemaker and transmitting ECG data to the outside world on command (present pacemakers are already capable of these functions). In addition, such a computer could completely process the ECG information locally, retaining examples of individual aberrant electrical events in an on-board memory for immediate or delayed transmission to the outside world and perhaps could also alter the details of its pacing function in real time based on its instantaneous analysis of cardiac electrical events. By the end of the decade, this same device technology should be able to support computerized hearing aids capable of converting the impinging acoustic energy into digital information and processing these data in real time to correct for the specific amplitude and frequency band deficiencies of the individual wearer. Such a device could also identify and suppress distracting loud noises and background rumble while selectively amplifying speech or music. Although computer programs and mathematical algorithms to perform such functions have existed for some time, present computers of sufficient capability are cumbersome and dissipate considerable power.

With the preceding short introduction to the world or integrated circuit design and fabrication, it is now reasonable to predict the manner in which this most fundamental of computer technologies will change the characteristics of the machines available for our use and alter the ways by which we solve biomedical problems. These issues will be discussed in the following sections.

Microprocessors

As noted earlier, of the several types of computers available in the commercial marketplace, the microprocessor has made the largest inroads into the biomedical world. The popular press representation that a microprocessor is a "computer on a chip" is correct, or nearly so, since in many cases no more than three or four such chips may be necessary to configure a full computer capability. In the early 1970s, with a rapidly increasing ability to fabricate more and more computer gates on a single silicon chip, designers attempted to compress the design of a then-typical minicomputer onto a few components. The first such devices, called 4-bit microprocessors, were barely capable of performing simple process control functions and possessed no arithmetic capabilities whatsoever. By 1974, however, a second generation of these devices, called 8-bit processors, demonstrated a quantum improvement in process control performance and the first usable arithmetic

capability. In 1978, another quantum jump was made to so-called 16-bit processors, the first devices worthy of the computer on a chip title. Lastly, in March 1981, a 32-bit computer was introduced to the user community as the first "micromainframe on a chip," a phrase intended to indicate that the flexibility, if not the brute speed of this new device (which contains 25,000 gates on each of three components), would exceed that of a present day conventional minicomputer and rival that of a full-sized mainframe machine (23).

Even with due compensation for vendors' publicity campaigns, it appears likely that the newest generations of such machines will to an increasing extent deliver large minicomputer performance for a hardware cost of a few hundred dollars. It is of interest that the largest impact of these new computers in the biomedical sciences will not be as controllers for machines, such as atomic absorption spectrometers, but in the guise of "home computer," which are definitely computers but have not exhibited the good manners to remain at home. Of the 290,000 personnel computers purchased in 1980 at a cost of over $1 billion, 45% were for the business market, 35% for home use, and 10% each for the educational and scientific markets (19). The power of these small units is astonishing, particularly since every one of the 290,000 machines sold in 1980 exploited second-generation microprocessor chips first announced in 1974; the fourth-generation microprocessor just introduced possesses at least 20 times the capability of the earlier devices. Not a single "home computer" exploiting even the third-generation microprocessor technology has yet been delivered (September 1981). Hence the performance of microcomputers observed to the present will be markedly enhanced during the next 5 years.

It is probable that microcomputers will rapidly become widely distributed within the biomedical research and diagnostic communities and will revolutionize the manner in which small computational tasks (requiring less than 1 million arithmetic operations/s) are performed. For example, during the first 10 months of 1981, staff members of the Mayo Institutions began to employ these devices in approximately a dozen applications (several of which may require more than one machine), spanning the three disparate enviroments of medical research, clinical practice, and administrative tasks.

Programmable Array Processors

The biomedical computational problems exemplified by the molecular, membrane, and fluid flow modeling studies and radiographic image processing described earlier generally require too much mathematical calculation to be assigned to microprocessors or even to minicomputers. These tasks require throughput rates of 5-25 million arithmetic operations per second at present and will demand 10-50 million operations per second in the future if overall processing durations are to be maintained at acceptable levels. Computational jobs of these magnitudes are frequently assigned to a specialized type of commercially available computer referred to as a "programmable array processor." Array processors generally execute all fundamental arithemtic and numerical functions except division but are usually unable to execute logical and decision-making operations. Hence such a machine is incapable of independent operation and must be employed as a "slave" to a minicomputer. The combined minicomputer-array processor "master-slave" combinations are capable of 5-15 million operations per second; unassisted minicomputers are hard pressed to attain 1 million instructions per second (2).

Array processors have proved to be useful for processing of moderate numbers of high-resolution (e.g., 2,000 × 2,000 pixel) images such as medical radiographs, or very large numbers of lower resolution (e.g., 512 × 512) images. They have also been employed extensively in X-ray and ultrasound CT and are being incorporated into computer systems for molecular modeling as well. The capacities of these programmable array processors will continue to increase, eventually fulfilling requirements for computation in the range of 100-500 million arithmetic instructions per second. The continued evolution of the power and the decrease in costs of such devices are being stimulated principally by the earth resources management programs for the processing of high-resolution multispectral imaging satellite data and by oil and minerals exploration groups for the processing of seismic data. The biomedical community will recognize the benefits of advances in array processor technology without having to support the expense of their development.

Special-Purpose Processors for Large Computational Problems

As a computational problem continues to grow it eventually exceeds the processing capacity of microprocessors, then minicomputers, and finally minicomputer-array processor combinations. At the present state of the computer art, when a given computational task requires more than approximately 20-50 million instructions per second to achieve processing durations that are reasonable with respect to the patience of a human observer, one possible solution is the development of a "special-purpose digital computer" whose design is carefully tailored to solve one specific computational problem (or at most a few such tasks) with high speed and high efficiency. This approach has been investigated extensively in our laboratories at Mayo Foundation; as described earlier, many CT processing problems, if performed on all the data available even from present generation X-ray and ultrasound CT sensors, would present truly formidable computational tasks (Table 1 and Fig. 4).

An example of a processor designed to solve a single type of difficult computational problem is a special-purpose computer under development in our laboratories to process the vast amounts of raw data generated by the research X-ray CT scanner described earlier, the Dynamic Spatial Reconstructor (DSR). The image cross-section reconstruction equations are exactly implemented in the computer hardware with a one-for-one correspondence. It is estimated that a complete processor of such a design will eventually achieve the 5 billion arithmetic operations per second, or 6×10^{12} gate • Hz, necessary to analyze a few seconds of collected DSR data within a few minutes (11).

Three principal advantages may be accrued from the development of a specialized architecture for particularly complex computational tasks. First, careful attention

to the operational details of the equations to be evaluated can always ensure that the specialized processor will contain the minimum number of integrated circuits necessary to execute the process to only the required level of arithmetic precision. Second, a specialized processor almost always exhibits maximum computational efficiency, since only those hardware elements necessary to execute the desired equations need be included in the design. Finally, the hardware can be optimized by means of detailed numerical "tricks" to guarantee maximum efficiency. These three features of a specialized computer design are of extreme importance when absolute compactness of the processor, achievement of the maximum possible computational capacity, or other operational constraints are of concern. Specially designed computers can in some cases be highly cost-effective. For example, it appears that a full-scale processor for the DSR can be fabricated for a parts cost of less than $250,000 in 1981 dollars; achievement of a 5 billion operation-per-second machine by any other approach would cost many millions of dollars, if feasible at all (11). Any requirements for computational rates greater than 1 billion arithmetic computations per second will probably mandate a specially designed computer, at least until the middle of this decade.

Conversely, specially designed computers are not without significant disadvantages. Such machines usually require a large amount of engineering effort, since each new procedure to be executed requires the development of an entirely new computer. The second disadvantage of a tailored architecture is identical with one of its advantages: its extreme efficiency is concomitant with an inherent inflexibility and resistance to reprogramming. In spite of these disadvantages, the specially tailored processors are likely to remain in evidence because, in some special cases, there is simply no other cost-effective method available to solve extremely large computational problems.

Large "Mainframe" Computers

The support of computationally demanding biomedical research tasks can, of course, be performed by large mainframe computers. Prior to 1967, the word computer was synonymous with this type of machine, a large extensive device requiring its own quarters, special cooling, and special installation but capable of performing really large computational solutions. With the introduction in the late 1960s of minicomputers, investigators could for the first time elect to rent the use of a large computer or to purchase a small computer and merely wait longer to execute their computational tasks "free of charge." By 1970 the early demise of the mainframe computer family was widely predicted.

Mainframe computers are still widely extant and for very good reasons. Such machines, generally costing $1 million or more (minicomputers are presently in the price range of $200,000–500,000) have maintained their value by providing major computational capabilities that no single investigator could afford and that minicomputers cannot offer. Most minicomputers are hard-pressed to perform more than 1-1.5 million operations per second and to support more than one or at most a few simultaneous users; conversely, mainframes can generate 300-400 million operations per second, are often optimized to execute scientific computations such as the solution of complex equations and can support several dozen users simultaneously. Machines that deliver (at a cost of $10-15 million) more than about 5 million operations per second are often called supercomputers; the largest and most modern of these machines can execute between 80 and 400 million operations per second (21). A recent study compared the performance-to-cost per computation ratio of numerous machines, from minicomputers to the largest supercomputers, and found the latter type to be by far the most cost-effective (2).

Though few facilities can afford to own such machines, their numbers continue to proliferate against all predictions. Hundreds of the less-than-5 million operations-per-second computers have been installed, and approximately 30 of the 80-400 million operations-per-second machines. In addition, access to these useful tools is proliferating much more rapidly than their numbers; advances in telecommunications technology now allow any potential supercomputer user to communicate with dozens of large machines from coast to coast for the purchase cost ($1,500) of a computer terminal and a telephone coupler. Researchers at the Mayo Foundation regularly employ the computational services of large mainframe computers in Boston, St. Louis, San Jose, and Ann Arbor; the Mayo Libraries regularly query by telephone national scientific data banks stored in computers in New York and Washington, DC. Conversely, Mayo Foundation computer resources are constantly in use by regional medical laboratories across the nation.

The power of these giant machines will continue to grow while the cost to use them per computing unit will continue to decrease. The biomedically oriented tasks assigned to supercomputers have already included experimental CT studies, modeling of blood flow in organs such as the kidney, calculation of stress and strain in the walls of the left ventricle of the heart, and studies of the three-dimensional motion of human joints (21). All of the large computers now in use were designed in the early-to-mid 1970s and hence did not benefit from the recent unprecedented advances in integrated circuit device technology described earlier. When the newest generations of super chips and new technologies such as gallium arsenide integrated circuitry become incorporated into the supercomputers of the late 1980s, completely general-purpose cost-effective computational power of 1 billion or more instructions per second will become widely accessible to the entire research community.

Computer-Aided Design, Manufacturing, and Test

The significant advances in technology described in the previous sections have also created a major liability for the designers of integrated circuits and computer systems. The increase in functional density on individual integrated circuits and the ever-increasing complexity of large computers are requiring enormous amounts of manpower to develop these devices. For example, the design of a well-known third-generation 16-bit microprocessor required 13 man-years, while a successor device, with somewhat more power though nonetheless a third-generation microprocessor, required 52 man-years of effort (3). A recently announced main-

frame computer required the efforts of numerous designers over a 5-year duration (24). The cost of manpower to design such complex systems is beginning to increase exponentially as the speed and complexity of such systems increase linearly. It is becoming continually more difficult even to control such massive designs, the largest of which already contain 250,000-1,000,000 gates and to be absolutely certain that each of perhaps 1 million or more connections have been correctly assigned.

Whether these gates and connections are physically distributed among thousands of small integrated circuits, as is presently the case for most large computers, or are, in the future, all placed on a small number of ultra-high-density integrated circuits, the designs of these systems have become too complex to develop within a reasonable duration using traditional paper and pencil methods. To mitigate this problem, there has been an increasing effort to develop specialized computer programs called computer-aided design (CAD) packages, which assist the engineers at every stage of the design, layout, and testing of a new processor or integrated circuit. By means of a high-resolution computer-controlled color graphics terminal, the engineer can construct the logical design of a single component, a subsystem, or the entire computer. Appropriate keyboard commands and a light pen or X-Y cursor allow individual logical building blocks to be retrieved from a preestablished "library" of components stored in computer memory and presented on the graphics terminal in the desired physical relationships. The designer then specifies the interconnections with the light pen, which are incorporated by the CAD program into a continually growing symbolic representation of the design; this process may be appreciated by a review of Fig. 8, sequence of photographs of the color video screen of the graphics design terminal in our laboratories at Mayo Foundation. As the process proceeds, the CAD program provides the engineering staff with intermediate information and partial results to allow the validity of the design to be verified continually. Following the initial design stage, these special software packages convert the symbolic representation of the new computer into a set of instructions for its physical fabrication. This "recipe" includes detailed information regarding component placement and connections on each circuit board, power supply, cooling requirements, and so on. Then, after fabrication of the machine, these same computer programs rapidly guide

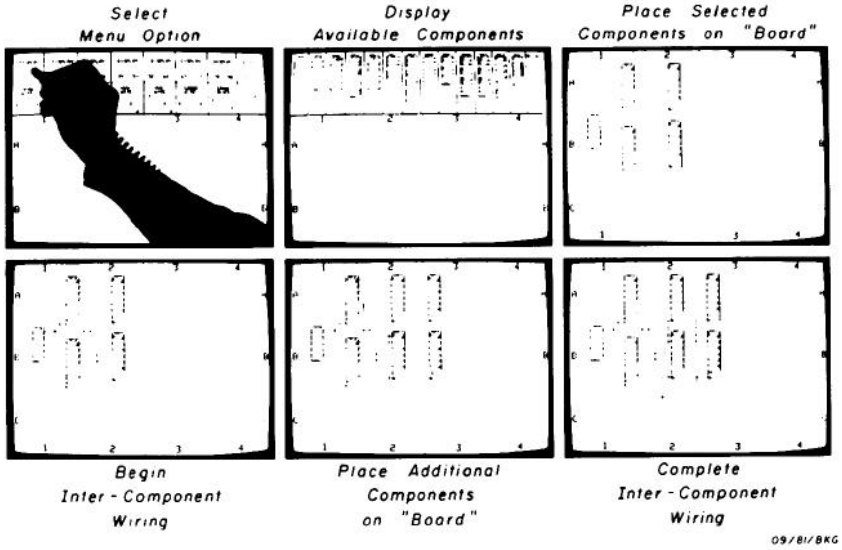


Figure 8
Six stages in the design of a digital system using modern computer-aided design hardware and software. Using an interactive computer graphics terminal, the designer "builds" and modifies the system by placing and interconnecting components. Manual drawing is not required.

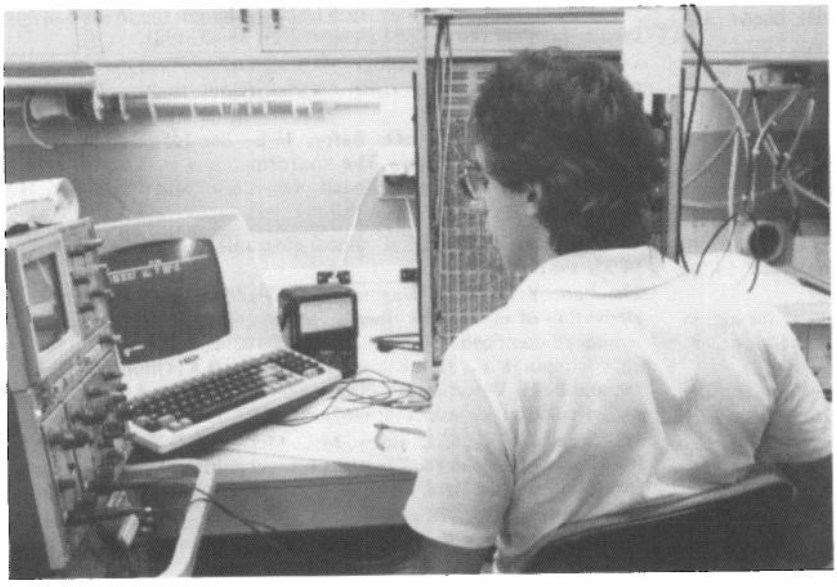


Figure 9
Operational testing of a new computer (up-ended on table) using modern techniques. Test pattern generators. oscilloscopes, and "logic analyzers" are now complemented by a computer terminal and associated keyboard; technician interacts with a computer-aided design program that guides verification of the new processor on a step-by-step basis.

the technicians through the initial testing procedure for the new machine on a component-by-component or even a connection-by-connection basis if necessary, decreasing the operational verification time from, in some cases, many months to a few days (9).

Perhaps of primary importance, CAD programs eliminate the paperwork burden, thereby allowing the engineer to concentrate on creative design tasks. In general, the efficiency and speed with which the design proceeds is markedly improved, since intermediate verification data that allow early detection of design errors are provided. In addition, the functional reliability of computers designed in this manner is usually high because the processors are constrained to a carefully prepared, consistent, and comprehensive set of layout and interconnection protocols. A large system developed by several engineers using manual methods usually reflects several sets of ad hoc design rules representing the unique experiences of the individual engineers. In addition, maintenance personnel generally can easily support such systems because a uniform and comprehensive set of documentation is available, a rarity when such material is produced manually by several different designers.

Summary

During the past decade numerous biomedical research and clinical specialties have become reliant on digital computers in the production or analysis of data; several new biomedical disciplines have actually come into existence only because of the power of the digital computer, e.g., computed tomography. In addition, several of these biomedical problems are so computationally complex that they rival the magnitudes of the largest numerical problems of the military world. All of the subsidiary disciplines of the digital computer technology are, however, rising to these challenges. As a result, computers of the 1980s will be able to satisfy the demands of the next generation of computation-intensive biomedical problems.

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Past President's Address

Four Decades of Physiology, Musing, and What Now

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The first fall meeting of the American Physiological Society was held at the University of Minnesota in 1948, and on this occasion, Dr. Wallace Fenn gave the first and certainly one of the best of the series of very excellent past presidential addresses that have followed during the ensuing 33 years (4).

Since I have had the privilege of hearing all but two of these addresses, all of which have been extremely well done, my most sobering thought on being informed of my election to the Presidency of our society was the realization that this would be my responsiblity at the 1981 fall meeting.

The title of Fenn's discussion was "Physiologists on Horseback." His concern at that time was that World War II had had a tremendous impact on the science of Physiology. He expressed his concerns in these words: "Suddenly Physiologists hace found themselves projected from their Ivory Towers into the marts of men. The 'long-haired boys' have left their laboratories and are out with the men on horseback in the military camps, in the sea, in the air, and in all the unfriendly environments from the equator to the poles."

Dr. Fenn was concerned that the associated bountiful financial support for physiological research, particularly of the applied variety, and the kudos that physiologists were enjoying at that time might subvert physiologists and physiological research in relation to basic but less glamorous problems.

Since my own career as a physiologist has spanned the decade prior to and the more than three decades that have elapsed since Dr. Fenn's address, certainly I can be categorized currently as one of the old boys in our profession. Furthermore, chronologically, if not on the basis of my very limited supply of wisdom, I am perhaps qualified to comment on developments in physiology during these four decades and even speculate to a limited degree as to the future.

At my age, I tend to remember old man stories. The lady leader of a delegation of Russian scientists to the recent International Congress on Gravitational Physiology in Innsbruck, Austria, topped off a series of old man stories told by various western delegates with this story.

It seems that a rather lively 80-year-old senior citzen succeeded in persuading a very vivacious 18-year-old young lady to become his wife. This feat accomplished, he became worried that he may have overstepped his physiological capabilities and so consulted his physician for advice concerning how best he could keep his young wife happy and satisfied with their marital status.

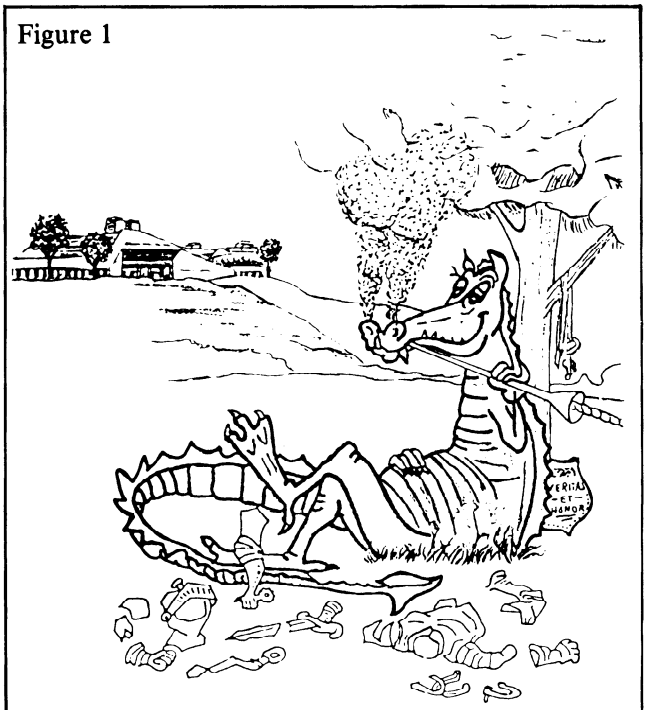
The physician recommended that the most certain way to do this was to find a young companion for the new wife, a suggestion which the aging groom proceeded to follow.

About a year later the physician upon meeting this patient on the street asked how his young wife was getting along. To which the senior citizen replied, "Everything is just fine; she is pregnant." So the physician asked the next logical question, "And how is her young companion?" and received the somewhat unexpected reply, "Oh, just fine; she is pregnant, also."

In any event, unexpected developments do occur in all phases of human activities including physiology. We are especially concerned with the latter tonight.

On the whole, I do not believe Dr. Fenn's worry concerning the materialistic subversion of physiologists and physiology has occurred to any practically important degree. Rather, I suspect most physiologists regard themselves as highly moral individuals who, like the knights of old, are doing their best for the greatest common good of man and animals alike. However, as exemplified in Fig. 1, sometimes the Good Guys lose the battle with such "dragons" as administrative bureaucracies, misguided study sections, journal editors, antivivisectionists, deans, or whatever other obstacles may block our paths.

Figure 1



Sometimes the Dragon Wins

[Used with permission of *IEEE Electron Devices Soc. Newsletter,* June 1981]

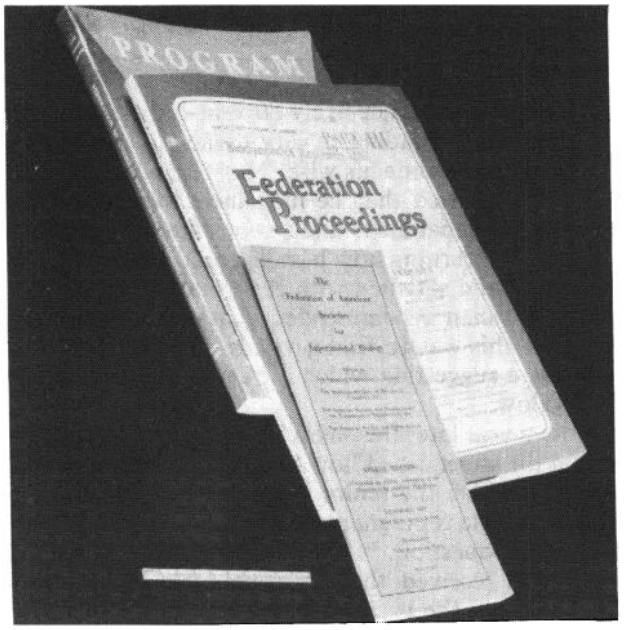


Figure 2

In any event, particularly since World War II, there has been a tremendous growth in all aspects of our discipline that merit consideration as to where we are going and why.

During the balance of these remarks, I would like to comment on three aspects of physiology: first, the growth of our society and its umbrella organization, the Federation of Societies for Experimental Biology (FASEB); second, government, particularly the National Institutes of Health (NIH), research fund granting mechanisms; and lastly, past and current developments in my own field of interest, namely cardiovascular-respiratory physiology and its future.

I attended my first FASEB meeting in 1938, 43 years ago. All of the scientific sessions were housed in a medium-sized building, the National Guard Armory of Baltimore. At that time, The American Physiological Society (APS) consisted of about 660 and FASEB about 1380 members as compared with about 6,000 and 20,000 members of these respective societies today.

A picture (Fig. 2) of the scientific programs for the 1938 meeting and the FASEB meeting held in 1979, 41 years later, in Dallas, provides a graphic impression of the relative sizes of these two meetings. The program for the 1938 meeting listed 604 abstracts as compared with 6,563 titles presented 2 years ago in the large convention center and multiple hotels in Dallas. A visual comparison of the small volume of abstracts published in the *American Journal of Physiology* in 1938 with the much larger two volumes of abstracts for the 1979 meeting (Fig.3) highlights the problem of increased membership of APS and FASEB, particularly the size of our meetings and the special unique values of very large versus small meetings.

Certainly there are unique values for both types of meetings, the relative importances of which are rated very differently by individual scientists.

Consequently, rather than the either/or solution that has been considered, the more logical solution is to sponsor and foster both large and small meetings. This FASEB, under the leadership of its Executive Director, Dr. Robert Krauss, is doing by sponsoring a series of Gordon Type Research Conferences, which will be held each summer beginning in 1982. The possibility of reducing the size of the spring meeting by adding a second large FASEB meeting in the fall is also being considered with different member societies as the primary participants in the respective meetings.

The projected increases in membership of our society and the other member societies of FASEB are plotted in Fig. 4, which suggests that APS membership will approach 10,000 by the end of this century. If no additional societies join FASEB prior to the year 2000, its predicted membership at that time will be about 38,000 (Fig. 5). Consequently, the problems associated with bigness will not diminish.

Our challenge is not to avoid bigness but to make it work to the advantage of the individual members of our society and the biomedical sciences on general.

Because of the increasing diversification of physiological disciplines, I believe APS should move progressively toward evolving into an umbrella organization covering all aspects of physiology. This evolution could and should be expedited by giving increasing autonomy to the current and future new sections of our society to the degree of allowing each section to set its own criteria for membership and election of its members, including holding independent meetings if it so desires.

Perhaps the most serious mistakes our society has made in the past has been being too restrictive in relation to its membership criteria. Historically, it is of interest that the split off of biochemists from our society and the associated formation of the American Society of Biological Chemists can be traced directly to the refusal of membership in APS of several young men whose major interest in those early days of this, then new discipline, was biochemistry. The names of these individuals you would recognize today as pioneers in the emergence of biochemistry into the powerful discipline it is at present.

Almost by definition the forerunners of new areas in the physiological sciences are to some degree mavericks

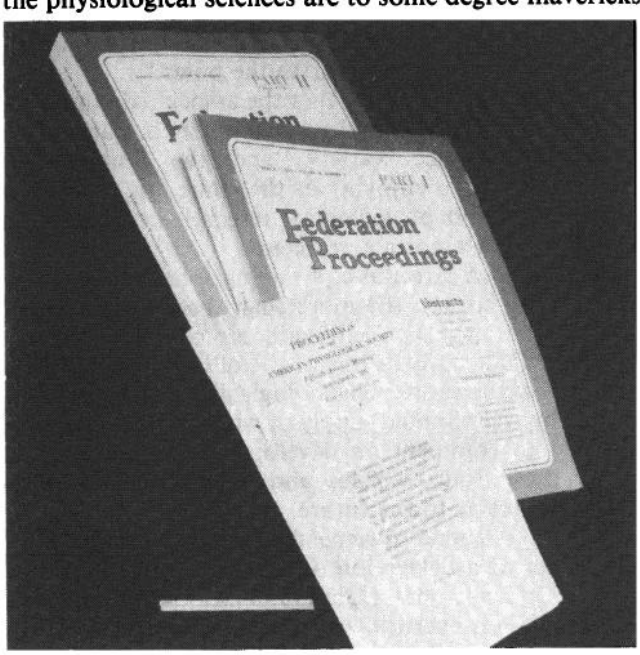


Figure 3

from the generally held concepts and interests of any particular era. Obviously, we should encourage forefront developments rather than antagonize what may develop to be the cutting edge of new areas of investigation. Without question this latter situation has occurred to some degree in more than one occasion in the history of our society. Encouragement of formation of new sections and affording them as much autonomy as possible seems the best way of minimizing such administrative mistakes in the future.

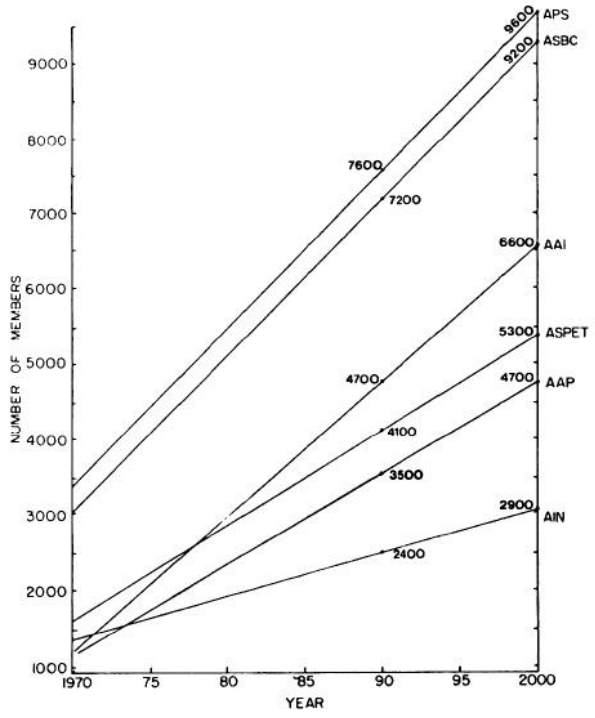
In my opinion setting up very restrictive criteria in the effort to restrict membership in a scientific society to an elite group of colleagues, as is the case particularly in some clinical investigative societies, is a subversion of the major purpose of a scientific society, which obviously should be to promote the advancement and dissemination of scientific knowledge and not as a badge of accomplishment of its individual members.

In the case of FASEB, I believe bigness in the terms of acting as an umbrella organization for as wide a spectrum of the life sciences as possible should be encouraged. In these days of increasing influence of federal and local governments in scientific matters as well as the opinions of the general public there is a real need for an effective umbrella organization to provide as much influence and clout as possible in the areas of government affairs and public opinion.

The very restrictive legislation relative to the use of experimental animals concerning which congressional hearings are now being held in Washington is a case in point. Figure 6 is a reproduction of pertinent sections of the House of Representatives Bill HR556, which carries the cleverly misleading title "The Research Modernization Act." Among other things, it specifies that 30–50% of all governmental research funds must be devoted to development of so-called alternative methods to the use of experimental animals.

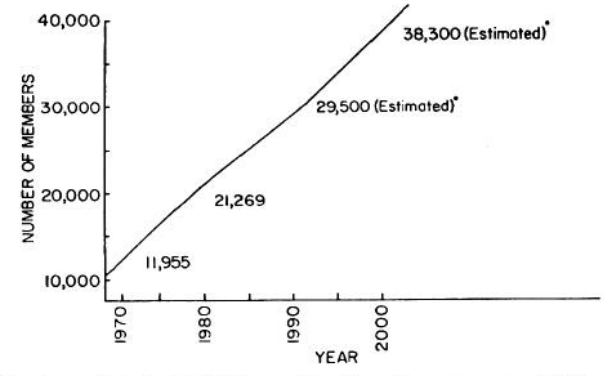
The repeal of pound laws that allow use by accredited laboratories of stray animals scheduled for euthanasia in local pounds has occurred recently in several states. The very active, and hence frequently successful, promotion of legislative proposals of these types by various well-organized and financed animal rights groups is perhaps the most serious threat to continued progress in the biomedical sciences and its offshoots, clinical medicine, and health care, which has raised its head over the span of the last 100 years (14,20). Efforts of individual scientists, including each of you, are of critical importance in combating these currently very vigorous movements that are basically antivivisectionist in character. However, a very strong umbrella organiza-

Figure 4



Projected number of members of 6 constituent societies of FASEB through year 2000. Projections are simply straight-line extrapolations of current membership growth.

Figure 5



Total projected FASEB membership through year 2000. *Calculations based on straight-line extrapolations of membership growth of 6 constituent societies.

Figure 6

97TH CONGRESS
1ST SESSION

H. R. 556

A BILL

To establish a National Center for Alternative Research; to develop and coordinate alternative methods of research and testing which do not involve the use of live animals; to develop training programs in the use of alternative methods of research and testing which do not involve the use of live animals; to eliminate or minimize the duplication of experiments on live animals; to disseminate information on such methods, and for other purposes.

SEC. 12. Effective in fiscal year 1982, each agency represented in the Center shall direct to the development of alternative methods of research and testing no less than 30 per centum and no more than 50 per centum of all appropriations made available to such agency for all research and testing programs conducted or sponsored by such agency involving the use of live animals.

tion on the scene in Washington is also required to maximize the probabilities of success on such endeavors.

Because the administration of the largest scientific umbrella organization in the US, i.e., the American Association for Advancement of Science, is mostly dominated by the basic physical, chemical, and mathematical sciences and various engineering disciplines, it is not a good representative of the life sciences.

FASEB, because of its reputation for excellence, particularly in Washington, its 69-year history of service to the biomedical sciences, and its strategically located, spacious, and very valuable Bethesda headquaters campus, is by far the best-suited organization to act as the representative of the Life Sciences. If properly constituted and run, FASEB can contribute to the well-being of its individual members, their various individual disciplines, and the biomedical sciences in general in ways both uniquely valuable and beyond the scope of independent society capabilities and furthermore in a cost-effective manner. In fact, FASEB is not "they" but in actuality FASEB is "us." This stems from the fact that the FASEB Board consisting of members from each of its constituent societies is the ultimate governing body of FASEB. It is this Board's responsibility to see that FASEB is indeed providing uniquely and maximally effective services at minimal possible cost to individual scientists and societies.

Observations, during the last several years as a member of the FASEB Board, of progressive developments stimulated in large part by questionings originating from our society have convinced me that this is being accomplished and that our efforts should be to stengthen FASEB rather than seperate from it as has been considered. In fact, the magnitude and scope as well as the cost-effectiveness of FASEB's sevices and contribution to the life sciences and the public good can be increased by increasing the breadth of FASEB's representation of the various life sciences disciplines, i.e., by adding new constituent or affiliate societies to its membership.

I believe liberalization of regulations for admission of new constituent societies to FASEB should be considered. FASEB's primary concern should be whether or not the applicant society is serving the members of its particular discipline, the biomedical sciences in general, and the common good of society in a meritorious and effective manner. If the answer to this question is positive, the criteria and methods of selection of members of such a society and other housekeeping and organizational matters, which are and should be the prerogative of each individual society, should not be a primary concern of FASEB. The breadth of the life sciences disciplines represented by FASEB can also be increased further by addition of affiliated societies whose purposes are compatible with those of the Federated Societies and who, for various fiscal or other reasons, are not prepared for full membership.

Along this same line possibly a majority of FASEB members would agree that the descriptive term "life sciences" is a better descriptor of the membership of FASEB than is "experimental biology." If so, perhaps a change of FASEB's name to "Federation of American Societies of Life Sciences," or some variation thereof, should be considered. This name, in addition to being a more accurate descriptor, because of its pragmatic overtone, is more conducive to recruitment of support from the general public, legislative bodies, industry, and benevolent foundations.

Furthermore, this designation would minimize apparent overlap between FASEB and the quite large biological umbrella organization, namely the American Institute of Biological Sciences (AIBS) and pragmatically indicate FASEB's closer relationship to human as well as animal life and the multiple aspects of the ever burgeoning and practically very important human and animal health care fields.

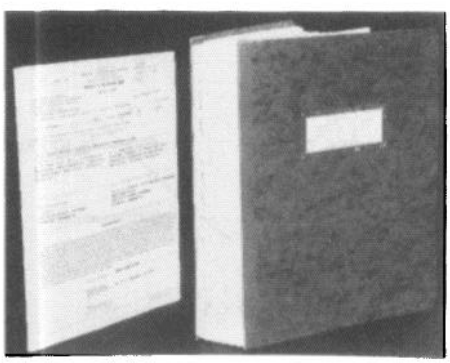
Enough of the societal-political aspects of physiology and other life sciences disciplines.

Current and future developments relative to governmental, particularly NIH support, of biomedical research and fellowships is of more immediate concern to most of us.

Perhaps the past and current situation in this regard can be concisely epitomized by Fig. 7, which is a picture, on the left, of my first NIH grant request submitted in 1957 and, on the right, a continuation request for support of the descendents of the original proposal, submitted in 1977, two decades after the primary request. Note that the original request, which covered only 13 pages, was for a modest (by current standards) amount and was approved at a level of $46,000 per year over a period of 5 years. Parenthetically, it is of historical interest that prior to 1957 the Mayo Foundation in order to preserve its independence had elected not to apply for extramural support for its research programs; also parenthetically, André Cournand was the chairman of the site visit team on this original request. In contrast to the 13 pages of the original request, the 1977 request covered 686 pages and was funded for 2.8 million dollars over a period of 2 years.

Perhaps the relative magnitude of the time and effort required by the researcher, study sections, and site visit teams alike in the "Good Old Days" of the 1950s and early 1960s as compared with the current situation can be appreciated by computing the dollars funded per page of these two grant requests. Back in 1957 the return in research funds per page of grant request amounted to $18,000 per page. This return was decreased fourfold to about $4,000 per page in 1977.

Figure 7



Pages	13	686
Submitted	1957	1977
Funded	$0.23 × 10^6 for 5 yrs	$2.82 × 10^6 for 2 yrs

IC/BI/EHW

National Institutes of Health grant requests

As I am sure you all are painfully aware, the grant situation is becoming increasingly grim and apparently this trend will continue indefinitely, so that a return to the degree of liberal grant funding that pertained in the 1950s and 1960s quite certainly will not return in my or any of your life times.

However, we can be certain (Fig. 8) that the process of congressional appropriation of funds will always be slow and that the probability of change in this aspect of governmental funding is very unlikely. The middle paragraph of this special notice which accompanied the notification of funding of the 1957 request reads as follows, "The appropriation bill for the new fiscal year that began July 1, 1958, is still pending in Congress; however, we have been authorized under a continuing resolution passed by the Congress to announce a limited number of grant awards." Some things, related to human nature and the political process in the United States' brand of democracy, apparently never change!

Enough of these disquieting comments. I would like to expend the balance of this discussion on things closer to my heart, namely the evolution of instrumentation and techniques for study of cardiovascular-respiratory dynamics past, present, and possibly future.

Since in his past president's address last fall, Ernst Knobil skipped over Harvey's contributions to circulatory physiology in favor of Harvey's less known but more biopsychologically stimulating contributions to reproductive physiology (7), perhaps a good place for me to start is with Steven Hales (Fig. 9).

Although no one can question the directness of Reverend Hales' observations, the desirability of permanent recordings, particularly of the dynamic aspects of the circulation that may occur too rapidly for the eye to follow, was obvious.

Perhaps Etienne Marey (Fig. 10), who was a contemporary of Claude Bernard in the latter half of the 1800s, was responsible for the greatest advances in the field of graphic recordings of dynamic events (13). Descendants of his smoked-paper kymographic recording assembly (Fig. 11) and many other of his inventions were the standard recording apparatus in physiology laboratories during the following 100 years as documented in Fig.

Figure 8

SPECIAL NOTICE

The National Institutes of Health is releasing award notices at this time only on continuation research grants that have beginning dates of July 1 or August 1, 1958.

The appropriation bill for the NIH programs for the new fiscal year that began July 1, 1958, is still pending in Congress as of this date; however, we have been authorized, under a continuing resolution passed by the Congress because of this delay, to announce a limited number of continuation grant awards.

Funds for continuation of your grant program may be obligated on and after the beginning date shown on the attached award notice, even though treasury check may not arrive by that date.

July 15, 1958

Figure 9

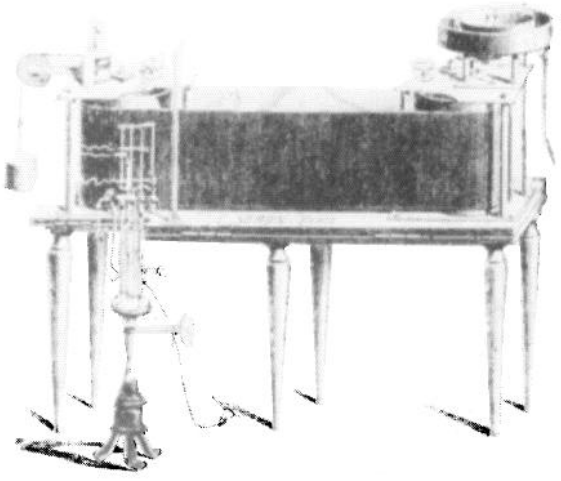
Stephen Hales (1728), Classics of Cardiology, Vol. I, Dover

Commissioned by Statham Instrument, 1967; *Classics of Cardiology*, Dover, 1941, vol. 1. [Reproduced with permission from Ref. 24]

Figure 10

Etieene Jules Marey (1830-1904)
[Museum Marey, Beaune, France]

Figure 11
Gravity-powered multichannel kymograph by E. Marey. [History of Medicine Museum, Paris]



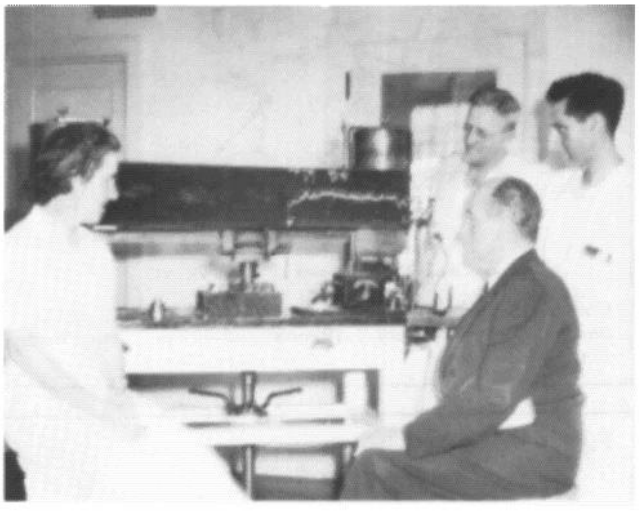
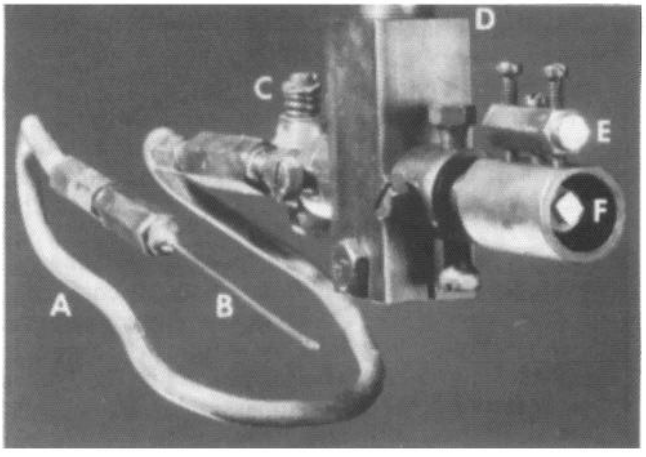


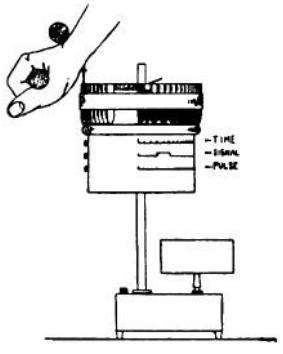
Figure 12
[Reproduced with permission from Ref. 19]

12. This is a picture of Dr. Hiram Essex, a former president of our society, examining a smoke-drum kymographic recording of arterial pressure recorded by a mercury U-tube manometer assembly used routinely in his and other physiology laboratories in the 1940s.

Obviously, the dynamic response characteristics of such systems are far removed from the requirements for a high-fidelity recording of cardiac mechanics or arterial pressure pulses. However, during this era Gasser and Erlanger had pioneered the use of the cathode-ray tube to record nerve action potential, and Hamilton had developed a high-frequency low-compliance membrane manometer (Fig.13) directly coupled via a water-filled malleable lead tubing to and 18-gauge needle for direct recording of arterial pressure. Hamilton also proposed and used the system illustrated in Fig. 14 for recording of arterial dilution curves of Evans blue in successive blood samples collected from blood flowing directly from the radial artery into a series of small test tubes mounted on a rotating drum. These devices were used in Cournand and Hamilton's cooperative studies of cardiac output in the early human cardiac catheterization experiments (3).

Figure 13
Courtesy of Dr. Philip Dow, Dept. of Physiology, Medical College of Georgia. [Reproduced with permission from Ref. 24]





From Hamilton, et al
Am J Physiol: 84
p 339, 1928

Figure 14
[Reproduced with permission from Ref. 19]

World War II intervened at this time, and as emphasized by Dr. Feen in 1958, the associated extensive use of high-performance military aircraft capable of flying at high altitudes and/or generating high accelerative forces was a very strong impertus for study of the pathophysiological effects of the environmental stresses of low atmospheric pressure, low oxygen tensions, cold, and high G forces on the healthy young pilots and crews of such aircraft.

The seriousness of the blackout problem at that time is illustrated in Fig. 15, which consists of frames from a motion picture taken in the sky over Rochester, MN, showing a passenger in a dive bomber losing consciousness and recovering therefrom during an exposure to a gravitational-inertial force environment five times greater than the force environment of planet earth.

Human centrifuges were built in Canada, the US, and the axis nations to study these phenomena under more controllable laboratory conditions. The first modern human centrifuge in the US, which was built and supported by private funds, went into operation in 1942 in the Medical Sciences Building of the Mayo Foundation in Rochester. Figure 16 is a picture of this device just

after its instillation in a specially built 40 ft-diameter circular room.

A human centrifuge is, in fact, a very large biomedical tool that, among other things, is uniquely suited for study of the compensatory and control reactions of the cardiovascular system as well as controllable degrees of cerebral and retina ischemia and respiratory ventilation-perfusion inequalities in awake human beings (27). Although at that time no one had that degree of foresight and the device was not built with that purpose in mind, this machine has had an important influence in new developments in the practice of medicine, particularly in cardiology and cardiac surgery.

Because humans are usually in the upright position, the responses of their circulatory systems to change in the gravitational-inertial force environment is much different, as you know, than animals. Consequently humans had to be used as the experimental animal in the human centrifuge.

This required development of new instruments more suitable for continous measurements of multiple physiological parameters, such as respiration, heartbeat, and blood pressure in healthy young men. Electronic transduction, i.e., generation of electronic analogs of these variables, was a mandatory requirement for these studies, since their monitoring and recording had to be carried out remotely from the whirling cockpit in which the subject was seated (Fig. 17).

The only recordings that could be registered in close proximity to the subject in the rapidly moving centrifuge cockpit were obtained by a movie quantitative instrumentation and telemetered recording techniques developed in the early 1940s to supplement motion pictures and subjective sensations are illustrated in the following figures.

Since loss of vision and consciousness during exposure to positive acceleration is caused respectively by lack of blood flow to the eyes and brain, measurements

Figure 15
[Reproduced with permission from Ref. 8]

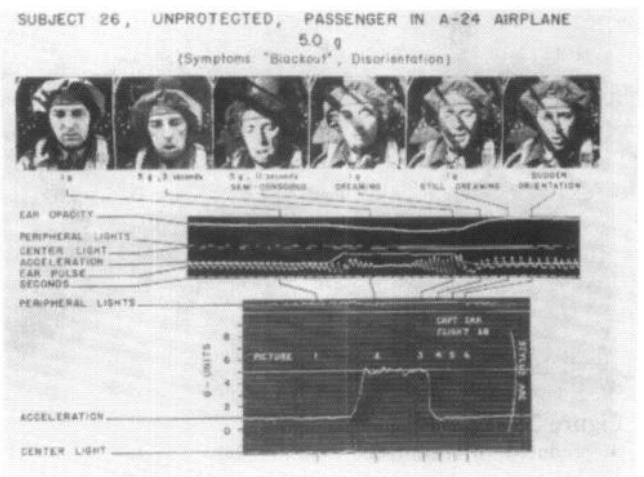
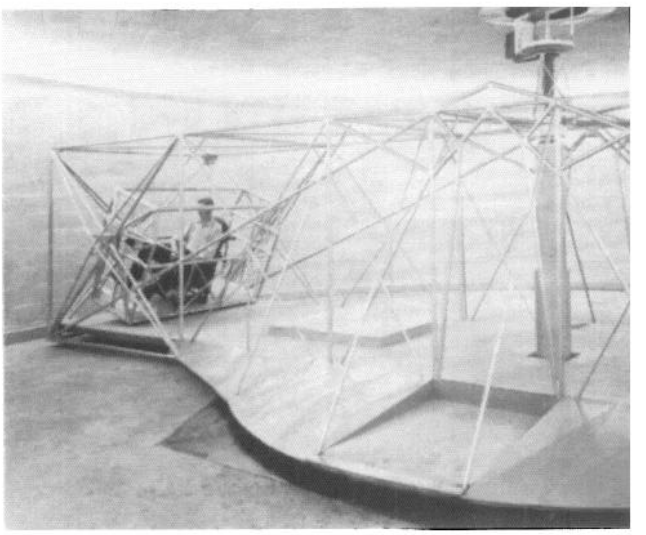


Figure 16



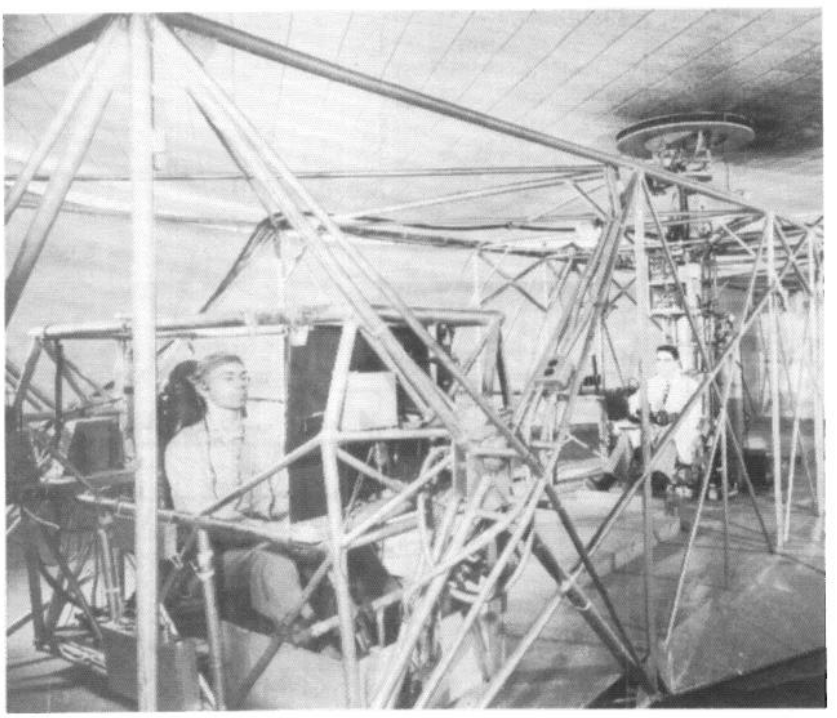


Figure 17
[Reproduced with permission from Ref. 19]

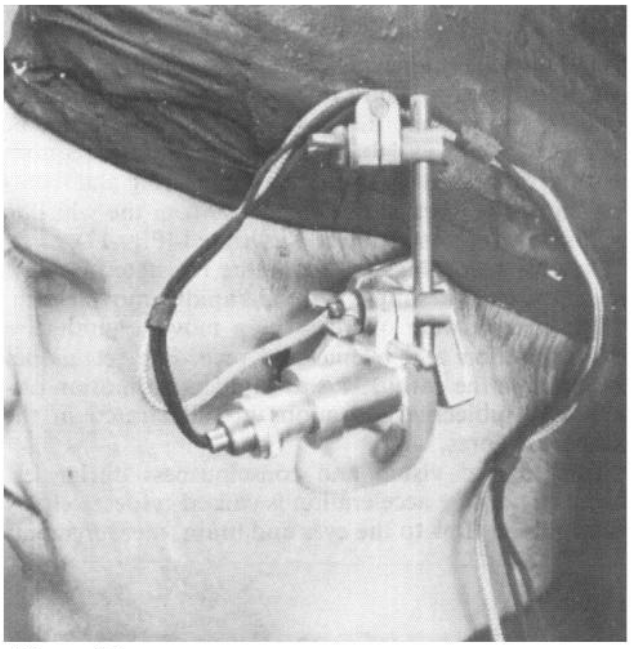


Figure 18
[Reproduced with permission from Ref. 23]

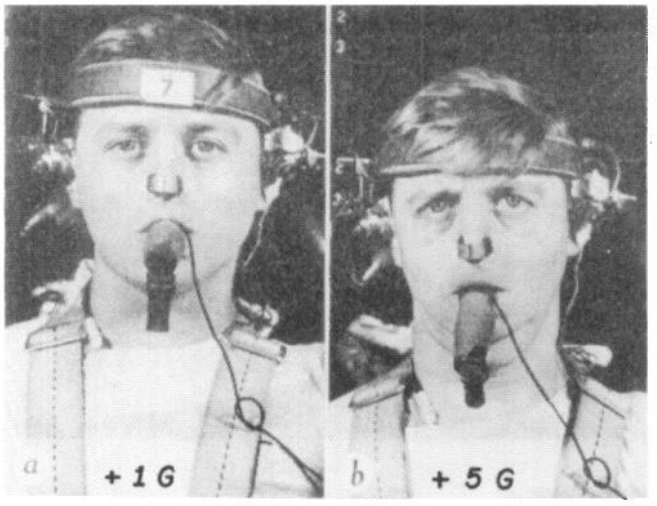
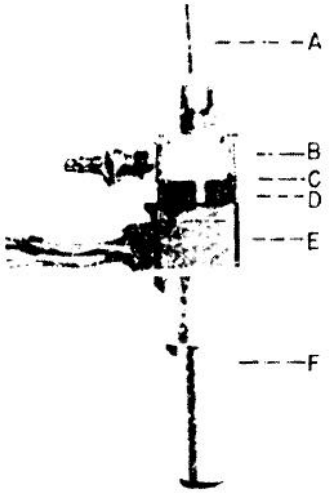


Figure 19
[Reproduced with permission from Ref. 17]

Figure 20



[Reproduced with permission from Ref. 24]

of parameters related to cerebral blood flow were of primary importance for human centrifuge studies. Photelectric plethysmography of the ear (Fig. 18) was used to study circulation to the head, simultaneously with respiration plus electrocardiogram and heart rate recorded from chest leads as illustrated in Fig. 19.

Since arterial pressure was of critical importance and it had to be measured remotely, the first strain gauge manometer (Fig. 20) for physiological pressure measurements was developed for direct recording of arterial pressure as illustrated in Fig. 21, which shows the assembly used for this purpose with Dr. Ed Lambert, who played a major role in its development, acting as the subject in the centrifuge cockpit (9).

A continuous simultaneous recording of 11 physiological variables is known in Fig. 22. These include arterial pressure at heart and head levels during an exposure to 4.5 G for 15 s. This type of recording in a human subject or even in an experimental animal was unique back in the mid 1940s and was a major basis for the very rapid developments in diagnostic right-heart,

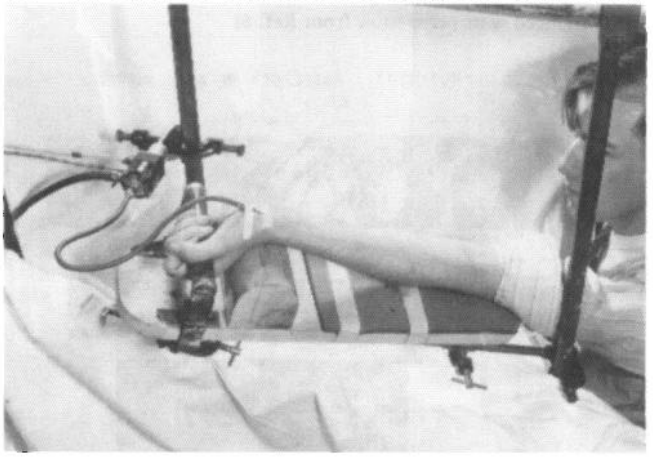
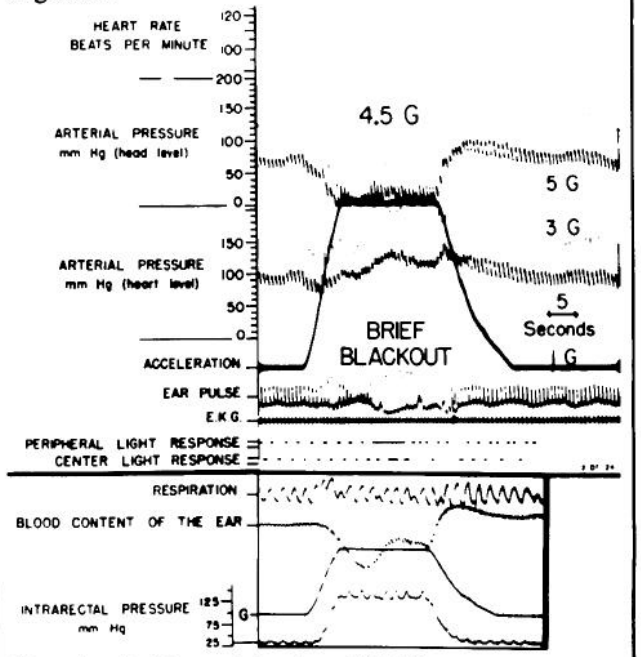


Figure 21
[Reproduced with permission from Ref. 24]

Figure 22



[Reproduced with permission from Ref. 15]

left-heart, and arterial catheterization techniques that occured at Mayo and elsewhere in the years following World War II (15).

A more real life impression of these human centrifuge and airplane studies can be obtained by viewing a series of colored motion pictures of instrumented human volunteers blacking out and losing consciousness on the human centrifuge and in a specially instrumented dive bomber during these World War II studies (2, 22).[1]

Rapid developments in intrathoracic great vessel and cardiac surgery in the late 1940s and early 1950s were a compelling impetus for continued improvement of the instrumentation involved in diagnostic cardiac catheterization and for cardiologist and cardiac surgeons to become familiar with these rapidly developing techniques.

Shortly after World War II, instrumentation developed on the human centrifuge began to be used in patients with congenital heart disease (Fig. 23). This earpiece oximeter provided the first noninvasive continuous quantitative recordings of arterial oxygen saturation at rest and during exercise in a treadmill (Fig. 24) (21). This was followed by the development of a monitoring and photokymographic recording assembly juxtaposed (Fig. 25) to the first human diagnostic cardiac catheterization laboratory at Mayo based on the recording and monitoring techniques developed on the human centrifuge. This assembly for the first time provided on-line real-time measurements of the oxygen saturation of blood during its withdrawal from a cardiac catheter or catheters (Fig. 26) as well as simultaneous pressure recordings from multiple intracardiac or vascular sites by means of cuvette oximeter-strain gauge assemblies (Fig. 27) (5).The increased facility and diagnostic accuracy provided by these real-time, on-line monitoring and measuring techniques revolutionized cardiac catheterization procedures over the breadth of this globe.

Development of these and other invasive methods for study of cardiovascular functions in humans that were stimulated by aviation medicine problems in World War II and gained great impetus with the development of human cardiac catheterization and intracardiac surgery in the 1940s attained perhaps the epitome of invasiveness in the late 1950s (16). Figure 28 shows the assembly of equipment for combined right-heart and aortic catheterization and simultaneous left atrial and left ventricular punctures so as to record pressures and dilution curves from all four cardiac chambers and across all four heart valves simultaneously.

Figure 29 is a thoracic roentgenogram of a patient undergoing these procedures in the clinical diagnostic laboratory located in and run by our Department of Physiology at Mayo (28). I think you will agree that this approaches the epitome of invasiveness as far as the chambers of the heart and the central circulation are concerned. These techniques, because of their complexity and degree of discomfort for the patient, were far from ideal. Furthermore, although we could give a great deal of quantitative objective information to the car-

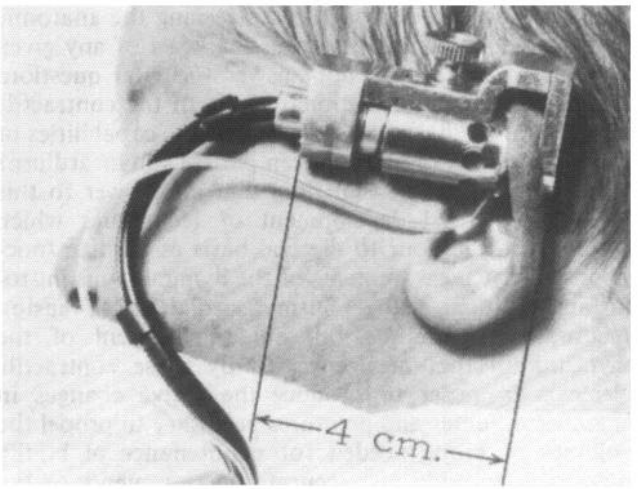


Figure 23
[Reproduced with permission from Ref. 26]

Figure 24
[Reproduced with permission from Ref. 26]

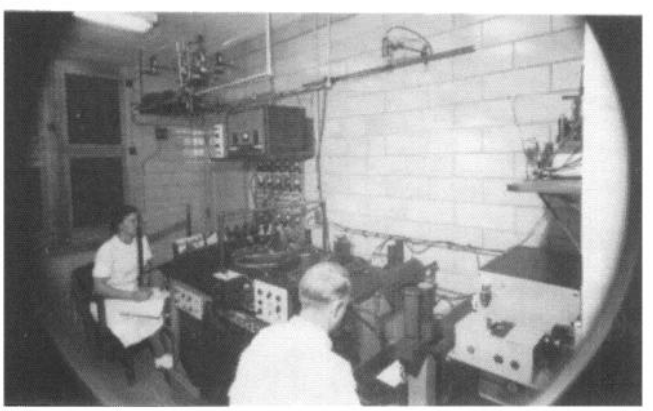


Figure 25

[1]These and other colored 16 mm motion pictures made on the Mayo Human Centrifuge and in a specially instrumented dive bomber (Figure 15) are on file in the archives of the Mayo Foundation.

diologist and cardiac surgeon concerning the anatomic defects and external function of the heart of any given patient, we still could not answer the vital question; namely what is the functional status of the contractile elements of the heart, i.e., the contractile capabilities or the cardiac reserve of any given patient's myocardium?

It became clear at that time that an answer to this question required development of techniques which would open the door to the real basis of cardiac function; namely, measurements of the dynamic, instant-to-instant, regional changes in myocardial length-tension relationships over the full anatomic extent of the myocardium that are generated by these contractile elements in order to produce the active changes in chamber bolumes and pressures necessary to propel the volumes of blood needed for maintenance of bodily functions. In addition, accurate measurements of the amount and regional distribution of coronary blood flow required to maintain the contractile capabilities of the myocardium were badly needed.

In the late 1950s and beginning of the 1960s, the only apparent possible means of obtaining this type of information by new or minimally invasive methods in intact animals or humans was to develop quantitative high spatial and temporal resolution roentgenographic techniques. This realization was the impetus for beginning the development of computer-based roentgen videodensitometric and videometric techniques for study of the circulation in our laboratory over 20 years ago (25).

After a series of intermediate steps over the next 10 years, the first system having the capabilities to solve this problem was designed and built in our laboratory (Fig. 30). It was a single X-ray source-video imaging chain assembly within which a dog supported in the head-up position was rotated mechanically in order to obtain the multiple angles of view required for the computerized mathematical reconstruction of multiple cross sections of the dog's thorax. This is, in fact, a high-speed synchronous volume-tric whole-body CAT scanner (6).

Figure 31 shows reconstructed cross sections of the chest of an anesthetized intact dog at cephalad, central, and caudal levels of the lungs during three different phases of the respiratory cycle. Although such images were unique when they were obtained nearly 10 years ago, because of the mechanical and hence slow circumferential scanning time, a single-source X-ray imaging system could be used for studies of cardiovascular and respiratory dynamics only under conditions of complete computer control of the heartbeat and respiration, a situation which is practical only in anesthetized animals.

Figure 26
[Reproduced with permission from Ref. 28]

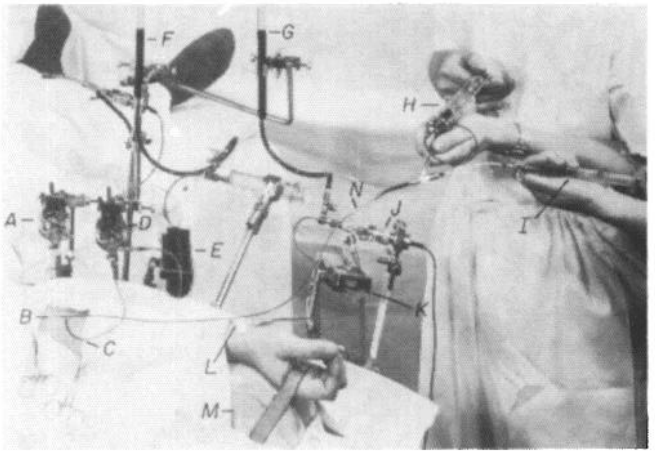


Figure 27
Cuvette oximeter, arterial sampling system. [Reproduced with permission from Ref. 19]

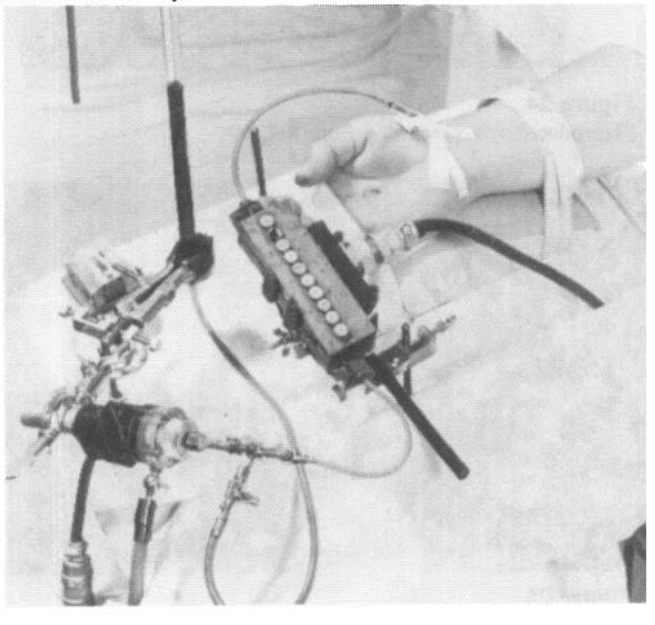


Figure 28
[Reproduced with permission from Ref. 16]

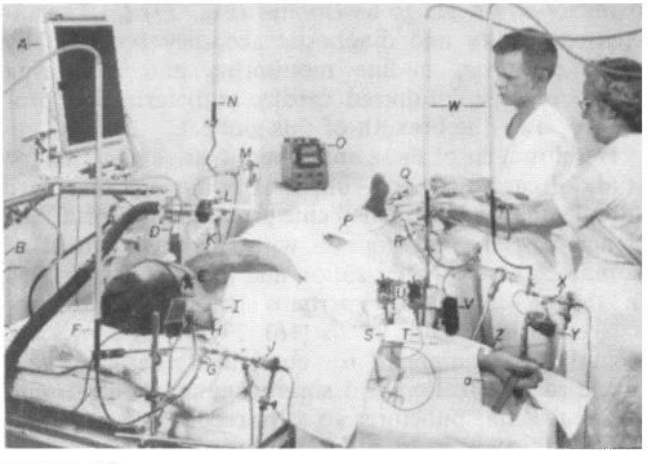
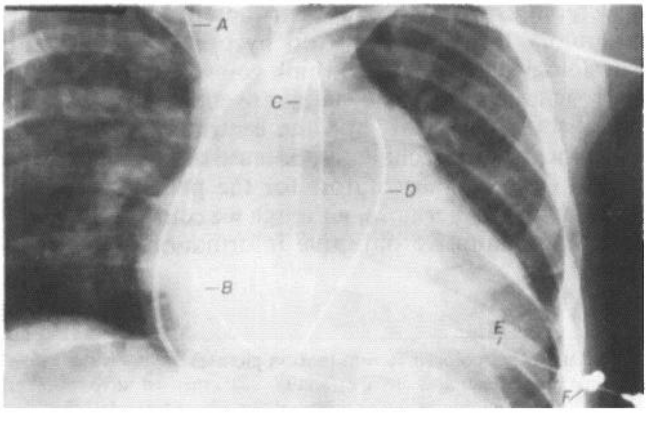


Figure 29
[Reproduced with permission from Ref. 16]



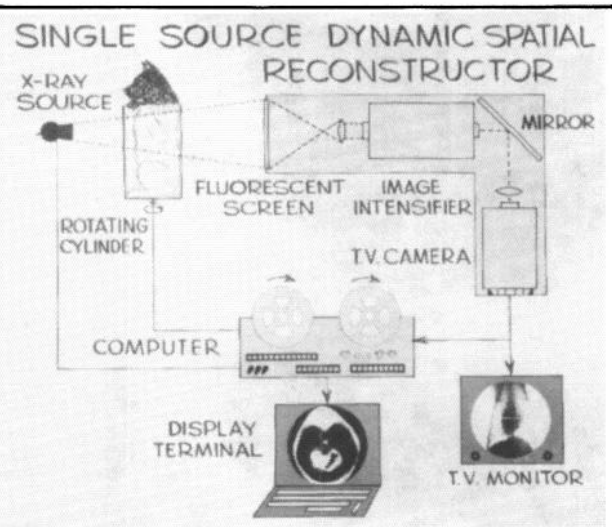


Figure 30
Single-source dynamic spatial reconstructor. [Reproduced with permission from Ref. 10]

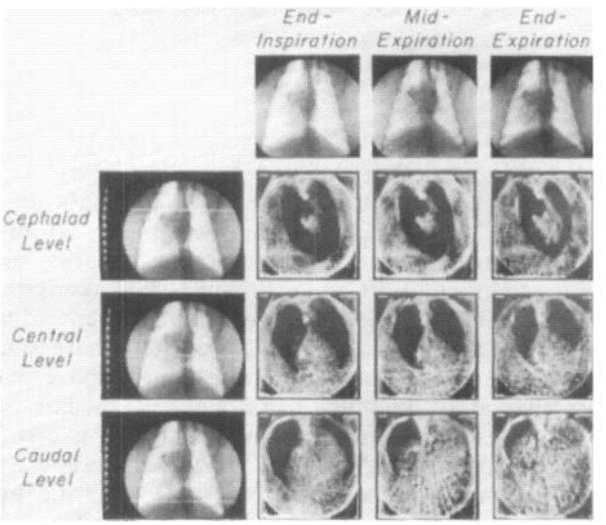


Figure 31
Phasic and cephalocaudal variations in thoracic cross sections reconstructed from 35 multiplanar roentgenograms of intact dog in water-immersion respirator. [Reproduced with permission from Ref. 11]

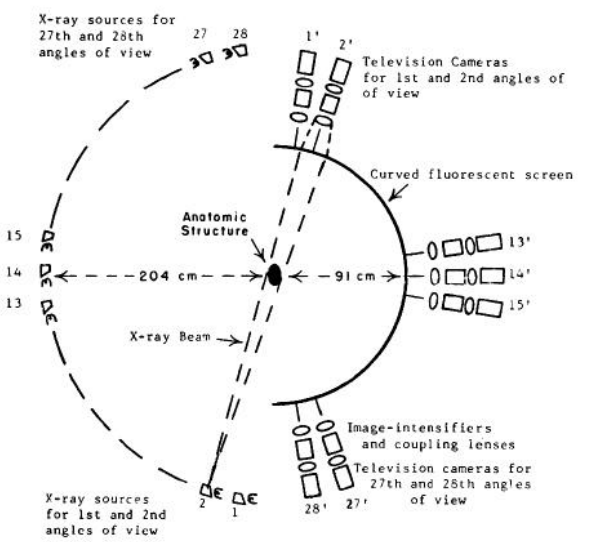


Figure 32
Diagram of DSR system.

Removal of this restriction for animal studies and a mandatory requirement for use in patients required a system with multiple X-ray video chains (Fig. 32) that could be scanned electronically in short enough periods to obtain stop-action, rapidly repetitive reconstructions of the dynamic anatomy and the regional distribution of the circulation and/or ventilation encompassing the full anatomic extent of the beating heart and lungs or other organs or regions of the body throughout individual cardiac beats or respiratory cycles, respectively.

This was an obvious idea at that time, but because of the high expense involved and the well-intentioned skepticism of our peer reviewers, much of the next five years was spent by some of us writing multiple grant requests and participating in many site visits designed to secure funding to build this big machine. Figure 33 is a picture of the multiple research grants and progress reports submitted to NIH since 1972 requesting support to build this machine and its associated and, equally important, computing and display facilities. These approximately six running feet of carefully written and multiply reviewed, retyped and rewritten about 10,500 typed pages, more than 4 million words, give some idea of the magnitude of the human and material efforts that have been expended by our laboratory group and the peer review mechanisms of NIH to bring the DSR project to its present status.

The top panel of Fig. 34 is an artist's conception, drawn about 6 years ago, of the results of these efforts. It is a new-generation whole-body X-ray scanner specially designed for noninvasive studies of the anatomical structural-physiological functional dynamics of the heart and lungs as well as vascular anatomy and circulatory dynamics in any region of the body. This machine, known as the Dynamic Spatial Reconstructor, or DSR for short, is, I believe, the most technologically complex and sophisticated instrument every designed and built specifically for biomedical purposes. The lower panel of Fig. 34, which is a diagram of the DSR on the left, followed rightward by the very powerful state of the art electronic data processing, computational, and computer-controlled display equip-

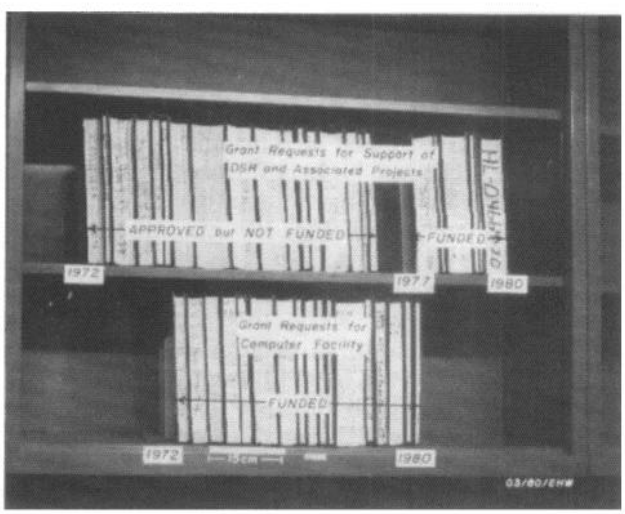


Figure 33
Unpublished documentation generated to obtain funding for DSR project.

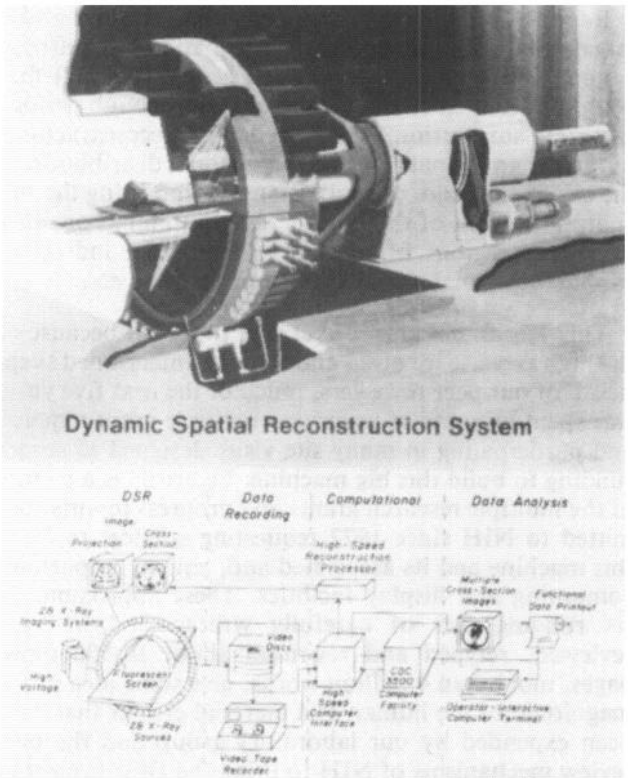


Figure 34
[Reproduced with permission from Ref. 1]

ment that are essential parts of this machine provides a better idea of the complexity of the total system.

Development of this machine required multidisciplinary high levels of expertise in physics, electronics, mathematics, the computer sciences, physiology, and medicine. The history of its development is of interest as an example of how things evolve in the biomedical sciences from unexpected and unpredictable beginnings. The beginning in this particular instance was the installation of a Human Centrifuge at Mayo during World War II to study blackout phenomena in healthy humans. Figure 35 documents the unfortunate (due to lack of space) removal in 1978 of the Mayo Human Centrifuge, to provide room, for the installation in 1979 of the DSR in its place. The capabilities of this machine can be best illustrated by moving television images of the beating heart and lungs and/or any desired sections thereof obtained by the efforts of the professional and technical staff in our laboratory, including Drs. Erik Ritman, Richard Robb, Barry Gilbert, Ralph Sturm, James Greenleaf, Lowell Harris, and many others (Fig. 37) using the techniques of noninvasive vivisection (18).

During the final segment of this dicussion, I would have liked to present some thoughts about "What Now"—that is the future in relation to various aspects of physiology and medicine. However, due to time constraints and because it is futuristic in tone, I will limit these predictions to just one area, space medicine. This, in spite of the fact that future developments in physiology and particularly clinical diagnosis and health care are just as exciting and of more practical importance.

Figure 36 is a drawing of the NASA space ship Columbia, which as you know made its initial Earth orbital

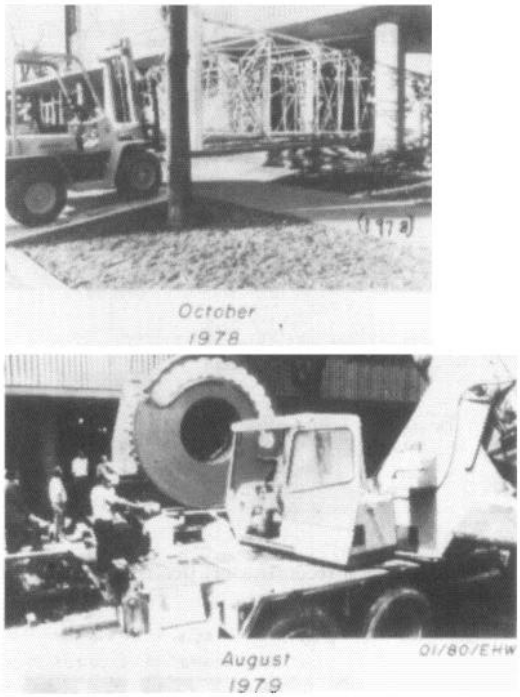
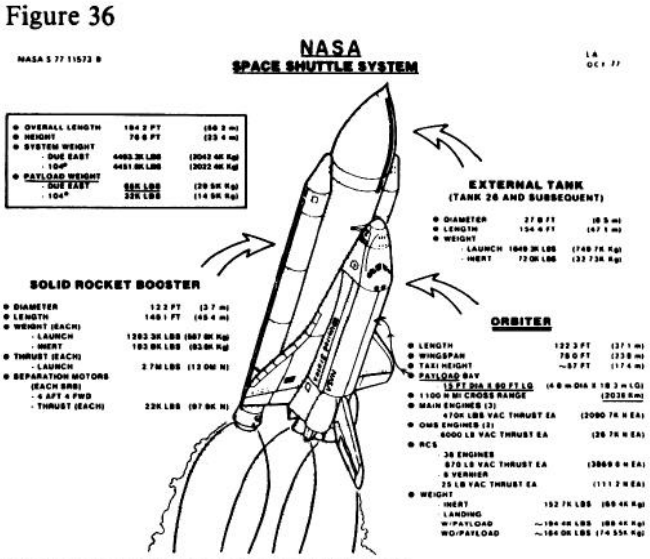


Figure 35

flights this year. The payload bay of this vehicle is designed to hold a space laboratory which can be up to 60 ft long, 15 ft in diameter, and weigh over 30 tons. This far exceeds the weight-carrying capacity and volume required to lift and maintain a DSR-like system and associated facilities in space. With the tremendous capabilities that Russia and the United States have to lift quite large and heavy structures into space and maintenance of complex man-operated facilities in Earth orbit for periods of many months, it is certain that the effects of long-duration exposures to zero gravity in humans will be of considerable scientific and associated technological and military importance.

The technique for noninvasive computerized vivisection and quantitative analysis of both the static and dynamic anatomic structural-functional relationships within any organ system of the body made possible by the DSR is ideally and uniquely suited for noninvasive

Figure 36



[Reproduced with permission from Ref. 19]

Figure 37

1. Erik Ritman; 2. Jean Frank; 3. Don Cravath; 4. Loren Krueger; 5. Robert Heethaar; 6. Julius Zarins; 7. Merrill Woodrow; 8. Don Erdman; 9. Michael Berggren; 10. Richard Robb; 11. Lowell Harris; 12. William Sutterer; 13. Peter Chevalier; 14. Ralph Sturm; 15. Steven Johnson; 16. Aloysius Chu; 17. Eiji Ino-Oka; 18. J. Bradley Kline; 19. Lourenco Gallo; 20. William Samayoa; 21. Ginny Brumm; 22. Irene Donovan; 23. Susan Skogen; 24. Don Hegland; 25. Sharon Zahn; 26. Jerome Sjostrand; 27. Diane Petefish; 28. Ronald Roessler; 29. Donna Balow; 30. James Greenleaf; 31. Barry Gilbert; 32. Earl Wood.

studies of the acute and chronic effects of zero gravity on the cardiovascular, respiratory, and skeletal systems of astronauts in space. Furthermore, fabrication of a spaceflight rated DSR-type system to carry out such studies using a space shuttle-space lab system is practical and will be feasible during the next decade.

Figure 37 is a picture taken several years ago of the professional and technical staff of the Mayo Biodynamics Research Unit. As this picture indicates, I have mostly acted as the cheerleader for this group. I cannot emphasize enough that the originality and independent thinking of each individual in this group have been a vitally important ingredient which has made possible whatever progress we may have made over the years.

In closing, although I cannot truthfully say it has been a pleasure to serve as your president during the last year, nevertheless it certainly has been an honor and a privilege. I would like to commend the following bit of advice from Saint-Exupery's *Wisdom of the Sands* (12) to Fran Haddy, your current President and his Council, "As for the future your task is not to foresee the future but to enable it."

Furthermore, as a representative of APS on the FASEB governing Board and particularly as its chairman this year, I also take this advice personally and very seriously. If there is one thing I have learned in my four decades as a physiologist, it is that none of us have the wisdom to foresee the future. Therefore, we should not expend much time in this regard because it largely is a futile exercise and consequently a waste of our most precious commodity, time. Rather we should do all we can to enable the future, particularly developments that promote the greatest common good. However, since we really cannot foresee with any degree of accuracy that these developments may be, we are more or less operating in the dark. Consequently, we should always keep in mind that new rules and regulations are very frequently promulgated to control or regulate future developments. Unfortunately, often rather than enabling the most desirable future developments, they restrict them by curtailing the liberties of individuals.

By and large, most individuals, particularly physiologists, are well meaning and, if given freedom to operate as they feel best, will work out, by trial and error or otherwise, the optimal solutions to problems as they arise. Usually such solutions are in the best interests of the greatest common good. That is the basic reason why free enterprise is superior to communism.

So Dr. Haddy and members of your Council, please do your best to enable the future of this great society and every individual in it. Best wishes to you all! Thank you.

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The campaign to eliminate the use of animals in research has been brought to the doorstep of the scientist.

Unlike previous campaigns, which were concentrated largely at the national level, individual scientists and institutions are now being confronted with well-orchestrated efforts initiated by humane and animal rights groups.

The move to the doorstep is not a shift in strategy by the antivivisectionists but, rather, a broadening of tactics designed to bring, at the grassroots, public attention to alleged abuses of animals by scientists. It is a move to gain, in part, those aims that cannot be achieved through Federal legislation or regulation and to display to the Congress the need for more stringent laws on the use of animals in research.

With this broadening of tactics the twin goals sought by the antivivisectionists appear to be 1) securing from the Congress mandates that would require the immediate replacement of all laboratory animals with alternative methods and 2) shutting off the supply of animals through the repeal of pound release laws and dealer restrictions at the state and local levels.

In an effort to attain the latter, humane organizations and animal rights groups in recent months have coordinated, supported, and initiated a variety of actions in the legislative and judicial bodies at the state, county, and municipal levels.

Although these efforts have not met with much success in state general assemblies, significant triumphs have been won at the local level. And in all but one case the victims of the antivivisectionists were academic institutions that depend on outside sources for their animals.

At the local and state levels the issues have been the repeal of pound release laws, the enactment of restrictive legislation, and courtroom decisions regarding the scientist's right to have laboratory animals.

Three Local Areas Targeted

At this time local initiatives have been targeted successfully by antivivisection organizations in three states: California, Michigan, and Maryland.

In Southern California the Los Angeles City Council recently repealed a pound release law that had been approved overwhelmingly by referendum when the issue surfaced 30 years ago. Now the Los Angeles County Board of Supervisors is considering a repeal of its pound release law and, if effected, will probably open the way for neighboring counties and cities in Southern California to consider similar actions.

The issues surrounding the Los Angeles City Council's repeal became somewhat secondary because much of the attention was centered on the Hollywood celebrities spotlighted in the movement.

However, scientists in Southern California have now formed a committee on animal research in medicine with the objective of stemming this tide as well as countering proposals that would establish review boards for all animal experimentation, require researchers to justify in advance any experiment being planned, and mandate a detailed protocol on animals for review prior to seeking any kind of grant support.

In Michigan proposals to repeal pound release laws are being won with less fanfare as antivivisection organizations are working county by county. Like there counterparts in Southern California, scientists there have formed the Michigan Society for Medical Research in an attempt to blunt this movement.

Local Issues in Maryland

The release of pound animals to research institutions is not the issue in Maryland, however. The challenge is a scientist's treatment of animals and the right to maintain the animals for experimentation. The final decisions on both issues are to be determined by the courts and will undoubtedly have an effect on researchers and their use of animals.

The president of a Washington, DC, animal rights group, who led a protest demonstration on the grounds of the National Institutes of Health in April, initiated in September a police search-and-seizure raid on a private reseach institution in Silver Spring, MD. The 23-year-old animal rights activist had worked for 2 months as a volunteer at the research institute that was using 17 macaque monkeys with deafferented limbs in a project to provide information on biofeedback in the absence of the usual sensory pathways.

The search-and-seizure raid by police, the first of its kind on a research facility in the United States, was made on the evidence of pictures and film taken by the volunteer after normal working hours and affidavits signed by members of humane organizations who visited the facility during the evenings.

The research director, a physiological psychologist, and his animal care assistant were arrested, and each was tried on 17 counts of animal cruelty. The 50-year-old director was found guilty for his failure to provide proper veterinarian care for six of the monkeys and was fined $3,000 ($500 on each count); this is being appealed. The animal care assistant was acquitted of all charges.

Several days after the conviction two civil suits were filed against the researcher and the institution by animal rights groups and activists as a means to block the return of the seized monkeys to the research facility. The monkeys have been held by court order at a facility of the National Institutes of Health.

Using legal arguments commonly invoked to prevent the return of battered children to their parents, the suits ask the courts to grant to the animal rights groups the legal status of "next friends" of the monkeys. The "next friends" status is given to persons to protect others who are incapable of protecting themselves.

It is believed to be the first attempt ever to have such status granted in a case involving animals.

Issues at State Level

At the state level, antivivisection organizations had two bills presented to the Missouri General Assembly that, if enacted, would have prohibited the use of live animals in public and private primary and secondary schools and would have prohibited the use of animals in experimentation by any institution within the state. The Virginia General Assembly passed a bill restricting dealers from supplying dogs to any institution outside of the state and limiting the sale of animals to only those approved institutions within the state. A bill to repeal the state's pound release law in Minnesota was rejected by the general assembly.

Aside from legislative and judicial avenues, antivivisection groups also are active in public demonstrations. In addition to the demonstration on the grounds of the National Institutes of Health, protest marches have been staged in San Francisco, Seattle, New York City, and Boston.

John M. Allman, a Caltech neurobiologist who uses monkeys in the study of the organization of the brain, recently wrote to *Science 81* magazine:

"Most scientists don't realize the danger. Such movements in the past—in this country, at least—have been largely efforts of small, fragmented, and relatively ineffective groups. But this new movement is carefully orchestrated, well organized, and well financed. Moreover, this is not just a local issue. It is going on intensively at the national and even at the international level. We'd be foolish to underestimate these people. They have clout. And if they attain their goals, it will effectively kill a lot of important research.

"People don't realize that we are already extensively reviewed. In my work I must follow the codes laid down by the National Institutes of Health and the American Physiological Society, among others. More than that, we are all required to keep detailed reports on all our animal experiments. And if pain or surgery is involved, we must tell them what anesthetics we used and in what dosages, what postoperative pain relievers and care were given, and so on."

Unlike the previous campaigns by the antivivisectionists, the activism of the 1980s can be expected to reach all levels of the scientific community. In fact, the antivivisectionists are already on the doorsteps of the scientists and their institutions.

William Samuels

Announcements

Honors and Awards

Nobel Laureate Andrew V. Schally, Department of Medicine at Tulane University, and an APS member since 1964, was awarded an honorary doctor's degree (J.D. Honoria Causa) from the University of Salamanca, Spain, 1981. The University of Salamanca is the oldest university in Spain and the third oldest in Europe. Since receiving the Nobel Prize in 1977, Dr. Scally has received twelve honorary doctorate degrees.

Are You Interested in Working in Space Biology?

NASA is offering several Research Associate Awards for scientists to work in laboratories capable of providing scientific advice and facilities relevant to Space Biology. The awards will vary from $14,000-$18,000 based on experience. They are planned for a 6-or 12-month period with the possibility of renewal. Proposals are due Apr 1 for Jul 1 funding and Oct 1 for Jan 1 funding. Eligibility: US citizens having Ph.D., D.Sc., M.D., D.D.S., of D.V.M. For information/application forms contact (*specify award date applying for*): Dr. X.J. Musacchia, Chairman NASA Award Committee, Graduate School, University of Louisville, Louisville, KY 40292, or Dr. Thora W. Halstead, Space Biology Research Associates' program, Life Sciences Division, NASA Headquarters, Washington, DC 20546.

MIT 1982 Summer Course Design and Analysis of Scientific Experiments

Massachusetts Institute of Technology will offer a one-week elementary course in Design and Analysis of Scientific Experiments, July 12–17, 1982. Applications will be made to the physical, chemical, biological, medical, engineering, and industrial sciences and to experimetation in psychology and economics. The course will be taught by Professors Harold Freeman and Paul Berger. Further particulars may be obtained by writing to the Director of Summer Session, Room E19-356, Massachusetts Institute of Technology, Cambridge, MA 02139.

MIT Selective Repository Guide

The Institute Archives and Special Collections Department of the Massachusetts Institute of Technology Libraries has issued a *Selective Repository Guide* (22 pages). The Archives is the repository for the manuscript and archival records of MIT, its faculty, alumni, and staff. The collections reflect the strengths of the research and educational programs of the Institute and therefore emphasize the history of contemporary science and technology and its impact on society. The guide is available for $2 from Institute Archives and Special Collections, Room 14N-118, Massachusetts Institute of Technology, Cambridge, MA 02139. Checks should be made payable to the Massachusetts Institute of Technology.

GUIDING PRINCIPLES IN THE CARE AND USE OF ANIMALS

(APPROVED BY THE COUNCIL OF THE AMERICAN PHYSIOLOGICAL SOCIETY)[1]

Animal experiments are to be undertaken only with the purpose of advancing knowledge. Consideration should be given to the appropriateness of experimental procedures, species of animals used, and number of animals required.

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in compliance with federal, state and local laws and regulations, and in accordance with the NIH Guide.[2]

Animals in the laboratory must receive every consideration for their comfort; they must be properly housed, fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during all surgical procedures. Where recovery from anesthesia is necessary during the study, acceptable technique to minimize pain must be followed. Muscle relaxants or paralytics are not anesthetics and they should not be used alone for surgical restraint. They may be used for surgery in conjunction with drugs known to produce adequate analgesia. Where use of anesthetics would negate the results of the experiment such procedures should be carried out in strict accordance with the NIH Guide.[2] If the study requires the death of the animal, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

_____

Investigator

[1]Revised 1980

[2]Guide for the Care and Use of Laboratory Animals, NIH Publication No. 80-23, Revised 1978, Reprinted 1980, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205.

PLEASE POST

American Medical Research Expedition to Everest, 1981

The American Medical Research Expedition to Everest took place in the fall of 1981. The chief objective was to obtain measurements of human physiology at extreme altitudes, and the expedition had considerable success. An extensive scientific program was completed, including some measurements on the summit of Mt. Everest itself (altitude 8,848 m, 29,028 ft); five people reached the summit; and everyone returned home safely.

The design of the expedition was very unusual. After one or two unsuccessful attempts to graft a physiological team on to a regular climbing expedition, we ambitiously decided to put together a special expedition with physiological research as its primary objective. Permission to go to Everest was given by the Nepalese government in June 1978 (obtaining permission is very competitive because generally only two or three groups are permitted on the mountain from the Nepalese side each year). Following this, the personnel of the expedition were chosen There were six highly experienced Himalayan climbers including John P. Evans, Climbing Leader. In addition there were six climbing scientists, all of whom were strong climbers, but each was an M.D. with an interest in high-altitude physiology. Their responsibility was to carry out the measurements at extreme altitudes. Finally, there was a third group of physiologists who worked in the two laboratories at Camp II (6300 m, 20,700 ft) and Base Camp (5,400 m, 17,700 ft).

Physiological measurements were carried out at four sites on the mountain. These were determined by the topography of Mount Everest as approached from the Nepalese side (see Fig. 1). It is relatively easy to walk to the Base Camp situated on the Khumbu glacier, but beyond that the route becomes very treacherous because of the steep unstable Khumbu icefall. This leads into a high, relatively flat valley, the Western Cwm, which was the site of Camp II (6,300 m, 20,700 ft), where the main laboratory was located. At the top of the Cwm is the headwall leading to the South Col, and about 200 ft above this was Camp V (8,050 m, 26,400 ft). Finally, a few measurements were done on the summit itself (8,848 m, 29,028 ft).

The diagram lists the main projects of the physiological program. The majority of the measurements that were planned were successfully carried out (indicated by check marks).

Summit (8,848 m, 29,028 ft)

Barometric Pressure and Temperature

These were obtained by Chris Pizzo, M.D. Final calibration of the barometer has yet to be done, but it is clear that the measured pressure was between 250 and 253 Torr. This is the first direct measurement of pressure on the summit and agrees well with predictions based on radiosonde meteorological data. However, it is about 15 Torr higher than the standard altitude-pressure tables would suggest. The temperature was -8.8°C, indicating relatively balmy conditions for the Everest summit.

Alveolar Gas Samples

Six of these were taken by Pizzo and the analysis is still in progress at the time of writing.

Continuous ECG

This was obtained on both of the medical summiters, Chris Pizzo and Peter Hackett.

Maximal Exercise Ventilation

Both Pizzo and Hackett obtained measurements on the way up to the summit from the South Col. Although ideally we would like to have more measurements on more subjects, the fact that any data were obtained for this ambitious project is remarkable.

South Col (8,050 m, 26,400 ft)

This work was actually done at Camp V, 200 ft above the South Col.

Maximal Work Capacity and Oxygen Uptake

This was the only project that was planned but not carried out on the expedition. Although both the science tent and bicycle ergometer were successfully carried up to Camp V, the winds proved to be so fierce that it was not possible to erect the tent. This was ironic, since this project was thought to be much less ambitious than the tests successfully carried out above the Col. Maximal work capacity was successfully measured on the Makalu Col (7,440 m, 24,400 ft) during the Himalayan Scientific and Mountaineering Expedition of 1960-61 but the winds were not so severe at that time.

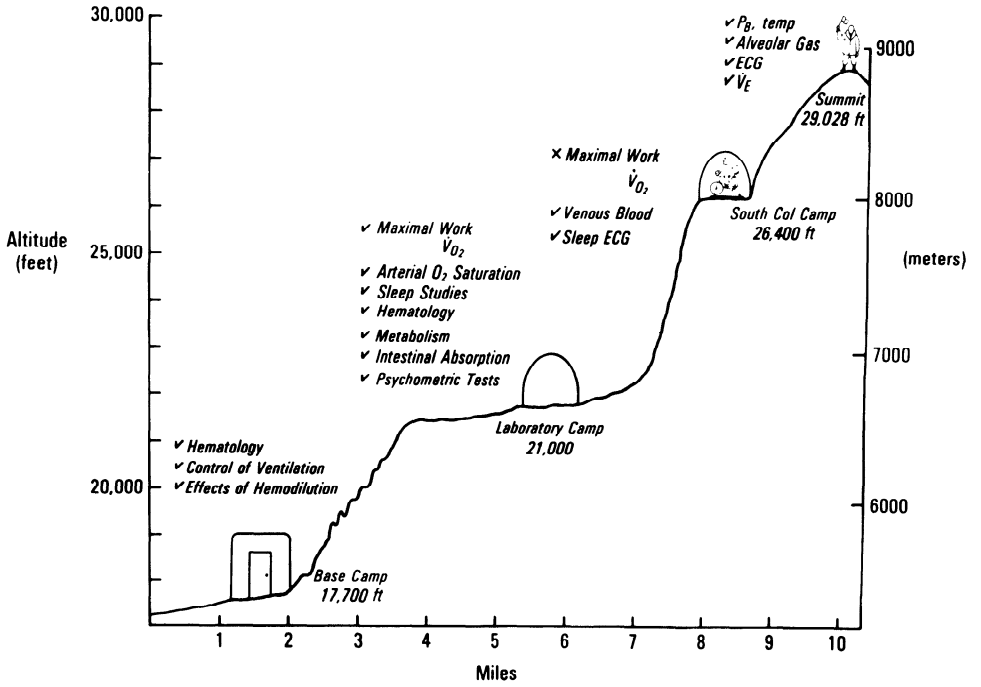
Venous Blood Samples

These were obtained on both Pizzo and Hackett during the morning after their successful summit climb. The samples were immediately taken down to Camp II, where they were analyzed for hematocrit, hemoglobin, red cell count, P_{50}, 2,3-DPG, and pH at a known P_{CO_2}. Knowing the alveolar P_{CO_2} from alveolar gas samples taken at the same time, it should be possible to determine the acid-base status of the arterial blood.

ECG During Sleep

Continuous recordings on a slow-running tape recorder were obtained from three climbers.

Figure 1



Main Laboratory (6,300 m, 20,700 ft)

Maximal Exercise with Arterial Oxygen Saturation (Including Inhalation of Low Oxygen Concentrations to Simulate Conditions on the Col and Summit)

Measurements were obtained on 12 climbers and scientists. In addition, six subjects were studied with an inspired oxygen concentration of 16% to give the same inspired P_{O_2} as the South Col. Two additional subjects were studied with an inspired concentration of only 14% to reproduce conditions on the Everest summit. Surprisingly high maximal work capacities and oxygen consumptions were found under both conditions, and the reasons for this are not known at present. Extremely low arterial oxygen saturations were measured by the Hewlett-Packard oximeter (less than 10% on one subject at the highest work level; however this is well below the range of accurate measurement of the device). The oximeter was directly calibrated at Camp II by means of arterial punctures on three subjects.

Sleep Studies

These showed marked periodic breathing with very low levels of arterial oxygen saturation (50% or less) following the apneic periods. ECG was recorded to determine whether there was a correlation between heart rate and respiration.

Hematology

Hematocrit, hemoglobin, P_{50}, 2,3-DPG, and blood lactate were measured on the venous blood of everybody at Camp II. Interestingly, the hematocrits were apparently not as high as reported on some previous expeditions. The reason for this is not known.

Metabolic Studies

Several samples of blood were taken from every subject at Camp II, and the plasma was frozen. The frozen samples were brought back to the United States and are presently being analyzed. Measurements with include fasting metabolic state, glucose tolerance, and hypothalamic-pituitary function.

Intestinal Absorption

Xylose absorption tests and fat and protein absorption tests were also carried out.

Psychometric Tests

Measurements of short-term memory, manipulative skill, and so forth were carried out and compared with base-line measurements made before and after the expedition.

Base Camp (5,400 m, 17,700 ft)

Control of Ventilation

An extensive program was carried out on hypoxic and carbon dioxide ventilatory drives in westerners and sherpas, both awake and asleep. An interesting finding was that some sherpas did not show periodic breathing during sleep.

Additional Hematology

Venous blood from a number of sherpas was analyzed, and the results should clarify this confusing area of physiology where there are a number of conflicting data.

Effects of Hemodilution

Four members of the expedition who had hematocrits of 58% and above had blood removed and replaced by human albumin solution. The results were assessed using bicycle ergometry and psychometric tests. No obvious changes were found, but further analysis is needed.

As indicated above, five people reached the summit. This would have been a notable success for a pure climbing expedition and was all the more remarkable for a

physiological expedition. Chris Kopczynski and Sherpa Sundare reached the summit on October 21, and 3 days later Chris Pizzo, M.D., and Sherpa Yong-Tenzing got to the top, followed a few hours later by Peter Hackett, M.D., in a solo climb.

Two sidelights on these climbs are of interest. Chris Pizzo had left his ice axe at Camp V when he was there a few days previously, but when he reached the camp, the ice axe was buried in the snow and could not be found. Having nothing better, he picked up a tent pole and doggedly headed for the summit with that. However, after climbing several hundred feet, he found an ice axe lying on the snow—a million-to-one chance. This was presumably left behind by a climber from a previous expedition who perished very high. Incidentally, an ice-encased body was encountered nearby—a grim reminder of the several people who have vanished on the upper part of the mountain over the years.

Peter Hackett had a lucky escape on the way down. Descending by himself in the chimney of the Hillary Step (a difficult obstacle not far below the summit), he fell. However, instead of ending up in Camp II, 2,600 m below, his foot caught on a piece of rock, and he found himself suspended upside down. He managed to extricate himself with the help of a fixed rope left by a previous expedition and eventually continued down. This was a remarkable escape.

Chris Kopcyznski, Chris Pizzo, and Peter Hackett were the ninth, tenth, and eleventh Americans, respectively, to reach the summit of Mount Everest.

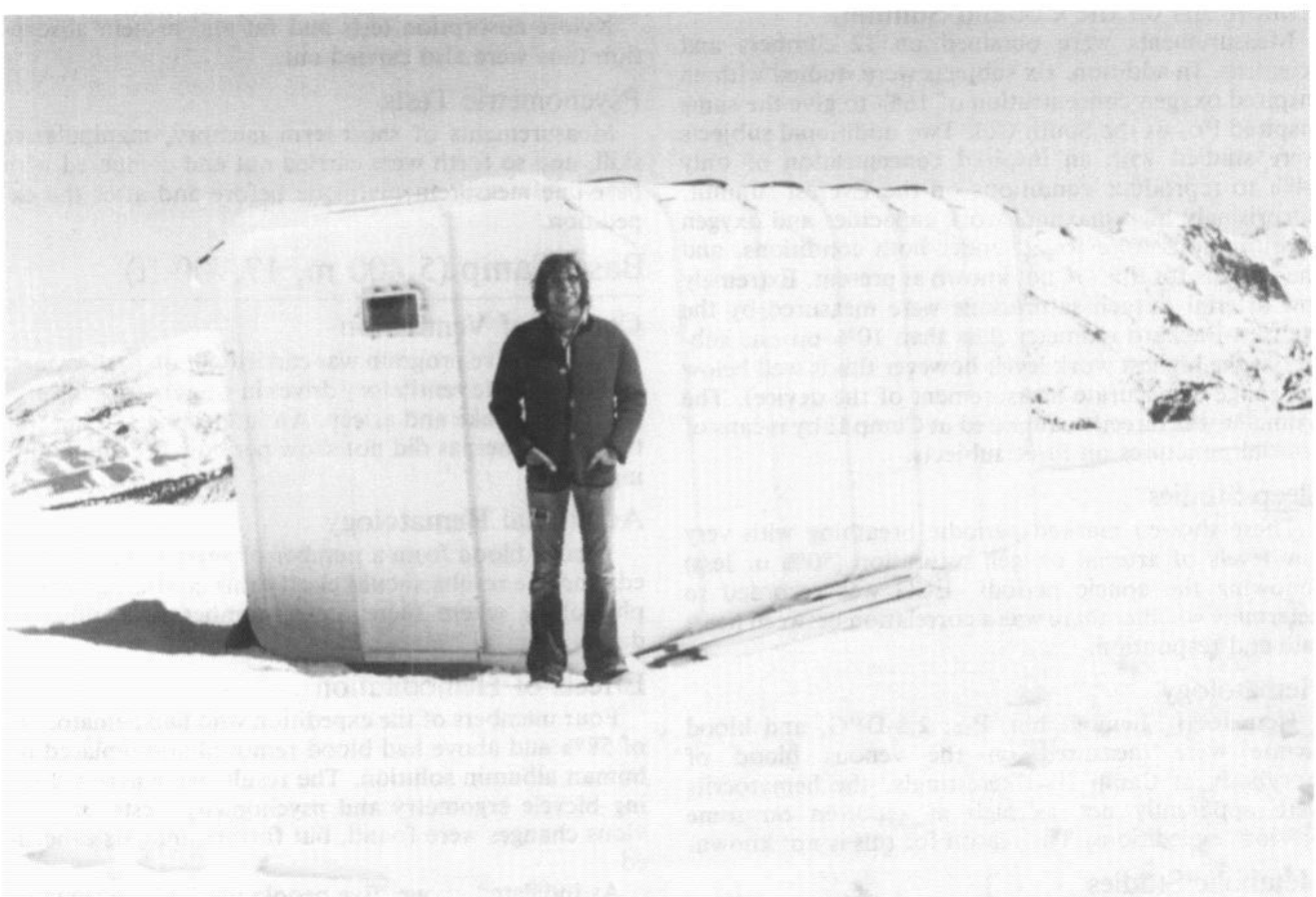
The expedition received grants from the American Lung Association, National Heart, Lung, and Blood Institute, National Geographic Society, National Science Foundation, Servier Laboratories (Paris), The Explorers Club, and the US Army Research and Development Command. Its sponsors included the American Physiological Society whose members made a number of cash donations.

John B. West
Expedition Leader

Portable Laboratory Hut Near Everest Available for Physiological Research

The American Medical Research Expedition to Everest left a portable laboratory hut in Pheriche, Nepal, near Mount Everest for use by future research expeditions. The approximate inside dimensions of the hut are 5 m long by 2.1 m wide by 2.1 m high. Construction is of rigid Klegecell (foam plastic) panels with a tough Kevlar skin, and the thermal insulation is excellent. The total weight is 600 kg, and it makes 35 porter loads to the Everest Base camp (5,400 m, 17,700 ft) or similar altitudes. A light bicycle ergometer is with the hut, but there is no other equipment. The hut makes an excellent physiological laboratory for high-altitude research in the field. For further details contact J. B. West, Section of Physiology, M-023, University of California, San Diego, La Jolla, CA 92093.

The portable physiological laboratory hut is presently stored in Pheriche, Nepal, near Mount Everest and is available for high-altitude physiological research.



Three Histories

Department of Physiology
Marshall University School of Medicine
Huntington, West Virginia 25701
1976–1980

In 1976, Dr. E. Aserinsky was appointed by Marshall University to chair and recruit a Department of Physiology and Pharmacology for the School of Medicine, which had just received the go-ahead signal in the form of a "letter of reasonable assurance" by the Liaison Committee on Medical Education. Dr. Aserinsky, who had just completed over 20 years of service at the Department of Physiology at Jefferson Medical College, began the major chore of selecting the first faculty for the department, thereby setting a precedent for the character of future appointments. The initial miniscule faculty included Dr. S. DeMesquita, who had served as a graduate student under Dr. Aserinsky, Dr. R.A. Brace, a former student of Dr. A. Guyton, and Dr. B.E. Watkins, who had worked with Dr. J.O. Davis. By the time the first medical students (24 in all) first arrived (January 1977), the Department of Physiology and Pharmacology was split into separate departments, Physiology under the leadership of Dr. Aserinsky and Pharmacology with Dr. D.S. Robinson as the head.

The research orientation of the first Physiology faculty was basically in two directions. One was toward the physiology of sleep, particularly oculomotor function and respiration; the other was toward the basic mechanisms of hypertension. This trend persists to this day (1980), even though there have been changes in the faculty. New additions include Dr. G. Wright from the National Institute for Occupational Safety and Health and Dr. S. Tzankoff from the National Institute of Gerontology.

E. Aserinsky

Department of Physiology and Pharmacology
School of Medicine
Universidad Central del Caribe
Cayey, Puerto Rico 00633

The School of Medicine of the Universidad Central del Caribe in Cayey, Puerto Rico, was inaugurated on September 8, 1976. A combined Department of Physiology and Pharmacology was established about 4 months later under the Chairmanship of Dr. E. J. Reininger. The following made up the initial staff: Professors Edward J. Reininger and J. Souto-Candeira and Assistant Professors G. Ehlert and D. Aggarwal. The area of Pharmacology was created on August 1977. Dr. B. Gothelf, from Dallas, TX, was appointed Coordinator of the course. Drs. Ehlert, Aggarwal, and Souto left about 1 year later, and Dr. W.C. De Mello, Professor and Chairman of the Department of Pharmacology of the University of Puerto Rico School of Medicine, replaced Dr. B. Gothelf as Coordinator of the Pharmacology course. Drs. Ehlert and Aggarwal were replaced by Dr. C. Font and Dr. J. Jované. These two left later: Dr. Font in May 1979 and Dr. Jovné in July 1980 to do an internship at the San Juan City Hospital. Dr. J. Santos Martínez, who retired from the School of Medicine of the University of Puerto Rico, replaced Dr. Reininger as Chairman of the Department on January 1, 1979. Dr. A. Fernández joined the Faculty in July 1979, and Dr. W. Lifschitz did likewise on January 1980. There is no graduate school at this University, and we therefore, do not have graduate students or postdoctoral fellows.

J. Santos Martınez

Physiology Department
Oral Roberts University Medical School
Tulsa, Oklahoma 74171
June 1977–August 1981

Discussions between officials of Oral Roberts University and the Association of American Medical Colleges concerning the possibility of establishing a medical school at Oral Roberts University began in the summer of 1975. Dr. J. Winslow was appointed as the first dean in 1976 and served in that capacity until June 1977, when he was appointed Vice Provost for Health Affairs. Dr. C. McCall succeeded Dr. Winslow as dean and served one year. He was succeeded by Dr. S. Garrett, the incumbent.

Dr. J. Norvell, previously Associate Professor, Department of Anatomy, Medical College of Virginia, was the first faculty member to be appointed. His appointment as Professor and Chairman of the Department of Anatomy became effective July 1, 1976. In October of that year, Dr. R. Herrmann came from a professorship in the Biochemistry Department at Boston University Medical School to become Professor and Chairman of the Biochemistry Department at ORU. On January 1, 1977, Dr. V. Scholes moved from South

Department Histories

One of the goals of the Centennial Committee is to catalyze the generation of a history of each physiology department in the domain of our Society. In October 1980, a letter was sent to 144 departments as a follow-up to a memorandum sent to department chairmen in July 1977.[1] In response, 79 acknowledgments were received stating that histories were being or had been prepared or were in some stage of preparation.

In this issue we are pleased to publish the first four such histories that have been submitted. One, by Horace Davenport records the early history of a relatively old department, founded at the University of Michigan in 1850. In telling us about physiology at Michigan, the author gives us many glimpses of contemporary events in other departments in the United States and in Europe as well. Thus the development of a department is placed in the context of the growing discipline of physiology.

The other three histories are by contrast all from very young departments. We thank Drs. E. Aserinsky, E.B. Brown, and J. Santos Martínez for providing histories respectively from departments founded at Marshall University School of Medicine, Huntington, West Virginia (1976); Oral Roberts University Medical School, Tulsa, Oklahoma (1977); and School of Medicine, Universidad del Caribe, Cayey, Puerto Rico (1977). Although these accounts understandably are brief in comparison to that of Dr. Davenport, they are nevertheless valuable. They establish important facts while they are still fresh and form a base for future writers who may continue them.

We thank the above authors for these histories. They have set an example, and we hope to receive many more departmental histories in the future. Authors may find some helpful hints in "Some Notes on Preparing a History of a Department of Physiology," by Horace Davenport, which appeared in *The Physiologist* 22(1): 30-31, 1979.

A.B. Otis

[1]The following articles on histories of Departments of Physiology were received prior to this letter: "The First Medical Physiologists at the University of Wisconsin" W.B. Youmans, *Physiologist* 18(3): 99-103, 1975; "History of the Department of Physiology at Southern Illinois University" H.M. Kaplan, *Physiologist* 20(5): 26-27, 1977; and "The Department of Physiology University of Saskatchewan" L.B. Jaques, *Physiologist* 21(5): 12-14, 1978.

Alabama Medical School to become Professor and Chairman of the Microbiology Department.

The Department of Physiology came into existence with the appointment of Dr. E.B. Brown, Jr., as Professor and Chairman on June 1, 1977. Dr. Brown had retired as Vice Chancellor for Faculties and Academic Affairs at the University of Kansas Medical Center prior to joining the organizing group at Oral Roberts University. As agreed at the time of his appointment, Dr. Brown remained in this position 3 years and retired July 31, 1980. He was succeeded by Dr. R. Bond, whose appointment began January 1, 1981. Dr. R. Armstrong, Associate Professor, served as Acting Chairman from August 1, 1980 through December 31, 1980.

The year following Dr. Brown's appointment was spent in recruiting faculty, ordering supplies and equipment for teaching and research, and developing the curriculum for the first two years of the medical course. Ten additional faculty appointments were made between August 1977, and August 1981. Nine of these eleven constitute the faculty at the time of this writing in the fall of 1981. The roster of all faculty appointed to the department with dates of appointment, school from which the doctorate degree was obtained, and previous position is given below in the order of their appointment:

E.B. Brown, Jr., Ph.D., University of Minnesota, 1949.
Appointed Professor and Chairman, June 1, 1977. Retired July 31, 1980.
Previous position: Vice Chancellor for Faculties and Academic Affairs, and Professor of Physiology, University of Kansas Medical Center.

J. J. Killion, Ph.D., University of Oklahoma, 1973.
Appointed Assistant Professor, Dec. 1, 1977. Promoted to Associate Professor, Aug. 1, 1980. Assistant Dean for Medical Sciences, Jan. 1, 1979 through Aug. 1, 1980.

C. D. Ross, Ph.D., Washington University, 1973.
Appointed Assistant Professor, Jan. 1, 1978.
Previous position: Postdoctoral Fellow, Department of Anatomy and Neurobiology, Washington University Medical School.

J.A. Cromer, Ph.D., University of North Dakota, 1972.
Apppointed Assistant Professor, Mar. 1, 1978. Promoted to Associate Professor, Jan. 1, 1979. Assistant Dean, Jan. 1, 1979 through Dec. 31, 1980. Resigned from Oral Roberts University, Dec. 31, 1980.

D.A. Godfrey, Ph.D., Harvard University, 1972.
Appointed Assistant Professor, May 1, 1978. Promoted to Associate Professor, Aug. 1, 1981.
Previous Position: Research Assistant Professor of Pharmacology, Washington University.

R.A. Armstrong, Ph.D., Washington State University, 1973.
Appointed Associate Professor, Jul. 1, 1978.
Previous position: Assistant Professor, Biology Department, Boston University.

D.F. Peterson, Ph.D., Kansas State University, 1970.
Appointed Associate Professor, Jul. 1, 1978.
Previous position: Associate Professor, Department of Pharmacology, University of Texas Health Sciences Center, San Antonio.
B.A. Sturbaum, Ph.D., University of New Mexico, 1972.
Appointed Assistant Professor, May 15, 1979.
Previous position: Assistant Professor, Department of Natural Sciences, Oral Roberts University.
M.H. Laughlin, Ph.D., University of Iowa, 1974.
Appointed Assistant Professor, Jan. 1, 1980.
Previous position: Aerospace Physiologist, USAF School of Aerospace Medicine.
R.F. Bond, Ph.D., Temple University, 1964.
Appointed Professor and Chairman, Jan. 1, 1981.
Previous position: Professor and Chairman, Department of Physiology, Kirksville College of Osteopathic Medicine.
J.A. Schwane, Ph.D., Kent State University, 1974.
Appointed Assistant Professor (part time) Aug. 1, 1978, (full time) Aug. 1, 1981.
Previous position: Associate Director, Human Performance Laboratory, Oral Roberts University.

As documented in this roster, two of the Physiology Department faculty members, Drs. Cromer and Killion, were recruited by the Dean to serve as assistant deans. Dr. Cromer left Oral Roberts University at the end of 1980 to become the dean at another institution, and Dr. Killion returned to the Physiology Department on a full-time basis August 1, 1980.

Physical Facilities

By August 1977, sufficient office space had been completed in the building that was to house the administrative offices and basic science departments of the medical school and dental school for the faculty then on the campus to move into the building. In March 1978, the area on the second floor designated for the Physiology Department was sufficiently complete for the four faculty members, one secretary, and one technician to move into permanent quarters. This area of 7,700 square feet of usable space consists of 15 offices, 16 research laboratories, shop, cold room, freezer room, and conference room. Student laboratories and lecture halls are in adjacent areas on the same floor. The student laboratories for physiology and pharmacology were designed for 64 students. Research laboratories were equipped in conformity with the requests of faculty members as they came on board. Excellent equipment has been provided for both research laboratories and student laboratories.

Teaching

When the medical school and dental school curricula were being planned, it was decided to teach Neuroscience as an integrated anatomy and physiology course. Drs. Dunn and Norvell from the Anatomy Department and Drs. Ross and Godfrey from the Physiology Department present these courses. All of the other organ systems are taught in separate courses for medical students and dental students.

The initial class of dental students began their program in August 1978. The Neuroscience course for this class was taught during the spring of 1979, and the Physiology course during the summer of that year. The first class of medical students began the medical course in December 1978. Both the Physiology course and the Neuroscience course were taught in the summer of 1979. The crowded schedule in the summer of 1979 was necessary to allow the medical class to complete the first year's work in time to begin the second year in August in line with the regular university calendar.

A two-semester Anatomy and Physiology course for students in the School of Nursing was being offered by the Natural Science Department prior to the establishment of the Medical School. This course was transferred to the Physiology Department at the beginning of the 1979-1980 academic year. The enrollment for this course is currently between 125 and 150 students.

With the initiation of the Master of Biomedical Science program in 1978, the Physiology Department established a series of graduate courses that are offered on a rotating schedule.

Research

Dr. Peterson was the recipient of a Career Development Award from the National Institutes of Health at the time of his appointment, and this CDA was renegotiated with NIH to continue at Oral Roberts University. Dr. Armstrong was in the process of applying for a substantial research grant from NIH at the time of his appointment. The grant was approved and funded and transferred to Oral Roberts University. The title of Dr. Armstong's grant was "Locomotion: Idling Metabolism and Gait Dynamics."

The first NIH grant awarded to a member of the Physiology Department while employed at ORU was awarded to Dr. M.H. Laughlin in May 1981. The title of this grant was "Exercise: Coronary Reserve, Coronary Heart Disease." In addition to equipping each laboratory as requested by the faculty member, those who did not have outside funding were provided with a research technician and a modest award, usually between $8,000 and $15,000 annually, to support research.

The Annual Report covering the 12 months ending July 31, 1979, lists titles of 25 papers published and 7 abstracts of presentations made at national and international meetings. The Annual Report for the year ending July 31, 1980, lists titles of 26 papers and 21 abstracts. To be sure, most of the contributions listed in the first Annual Report were of research carried out at other institutions by faculty prior to joining the department at ORU. This is also the case for many of those listed in the second Annual Report. These data, however, do indicate that the faculty are research oriented and productive.

E.B. Brown, Jr.

Honorary Members

Honorary Members of the American Physiological Society are distinguished scientists outside of North America who have contributed to the advancement of physiology. The Society has elected thirty-five scientists to Honorary Membership, and the date of their election is given.

E.D. Adrian†, Cambridge, UK (1946)
E. Braun-Menendez†, Buenos Aires, Argentina (1959)
F. Bremer, Brussels, Belgium (1950)
A. Dastre†, Paris, France (1904)
P. Dejours, Strasbour, France (1981)
Sir John C. Eccles, Canberra, Australia (1952)
T.W. Engelmann†, Berlin, Germany (1904)
R. Granit, Stockholm, Sweden (1963)
R.A. Gregory, Liverpool, UK (1981)
E. Gutman†, Prague, Czechoslovakia (1971)
A.V. Hill†, London, UK (1946, 1950)
Sir Alan L. Hodgkin, Cambridge, UK (1952)
F. Hofmeister†, Strasburg, Germany (1904)
B.A. Houssay†, Buenos Aires, Argentina (1941)
A. Hurtado, Lima, Peru (1959)
A. Huxley, London, UK (1981)
H.E. Huxley, Cambridge, UK (1981)
G. Kato†, Tokyo, Japan (1965)
A. Krogh†, Copenhagen, Denmark (1946)
Y. Kuno†, Toky, Japan (1959)
J.N. Langley†, Cambridge, UK (1904)
L. Lapique†, Paris, France (1946)
C. Monge†, Lima, Peru (1952)
G. Moruzzi, Pisa, Italy (1959)
L.A. Orbeli†, Leningrad, USSR (1946)
I.R. Pavlov†, Russia (1904)
E. Pflüger†, Bonn, Germany (1907)
W.T. Porter†, Dover, MA (1948)
F.J.W. Roughton†, Cambridge, UK (1957)
Sir Edward Sharpey-Schaefer†, UK (1912)
Sir Charles Sherrington†, Oxford, UK (1904)
H.H. Ussing, Copenhagen, Denmark (1959)
K. von Frisch, Munich, Germany (1952)
C. von Voit†, Munich, Germany (1907)
H.H. Weber†, Heidelberg, Germany (1959)

†Deceased

To F.J. Haddy:

I received with the greatest possible pleasure yesterday your letter of 28 October informing me that the American Physiological Society has elected me to Honorary Membership.

I deeply appreciate the rare and outstanding honour your distinguished society has thus conferred upon me; at the moment of writing I only wish I could feel more worthy to join my thiry-one predecessors whose names are so well-known in physiological science the world over.

May I remark that it is also a great personal joy to me to be thus honoured because of my esteem and affection for your country and its scientists, ever since I was a student of Doctor Ivy's at Northwestern, as a Rockefeller Medical Fellow in 1939.

R.A. Gregory
Emeritus Professor of Physiology
University of Liverpool
Liverpool L69 3BX, UK

To FJH:

I was absolutely delighted and greatly honored to learn that the American Physiological Society has elected me to Honorary Membership, especially when I scan the list of names of previously elected members. I will of course accept your offer of membership with great pleasure and look forward to enjoying the various advantages and attending some meetings.

Thank you again very much.

H.E. Huxley
MRC Laboratory of Molecular Biology
Cambridge CB2 2QH, UK

To FJH:

I received today your letter of October 28.

I am very happy to have been elected Honorary Member of the American Physiological Society, and I wish to express to you and to your colleagues my most sincere gratitude. Indeed it is a honor to be admitted in such a restricted group of famous physiologists.

My ties with the American physiologists are already ancient, since I was an immediate pupil of Wallace O. Fenn in Rochester, NY, in 1951-1952. Since then, my scientific relations with my American colleagues increased steadily; this year I visited the States four times.

My ties are not only professional. My wife is an American citizen and did her Ph.D. thesis under the supervision of David Hubel and Torsten Wiesel, who are our close friends. That is to say that my wife also prizes the distinction attached to my nomination to the Honorary Membership of the American Physiological Society.

The long list of attributions of a Honorary Member is impressive, and I am very thankful for your generosity.

I do hope to have in the near future the opportunity to express to you viva voce all my thanks.

P. Dejours
Director, Laboratoire de Physiologie Respiratoire
67087 Strasbourg, France

APS Sections

How to Become Affiliated

In compliance with the Society's bylaws, a number of sections have been organized encompassing various physiological specialty interests. These sections advise the Society on matters of interest to the specialty represented by the section, assist the Society in organizing scientific meetings, and nominate individuals for membership on Society committees.

Membership in the sections is open to all members of the Society. However, the Statement of Organization and Procedures for each section establishes specific requirements for membership. APS members who wish to become affiliated with one or more of the listed sections should comply with the requirements noted following the named section. The reference shown beneath the name is the issue of *The Physiologist* where that section's Statement of Organization and Procedures has been printed.

Cardiovascular
23(5): 5, 1980. Send a letter requesting affiliation to the Membership Services Department of APS

Cell and General Physiology
24(3): 35, 1981. Same as Cardiovascular

Comparative Physiology
20(6): 14, 1977. Indicate a primary or secondary Interest Area Code 10 on the Membership Records Questionnaire

Endocrinology and Metabolism
23(5): 8, 1980. Same as Cardiovascular

Environmental, Thermal and Exercise
20(6): 15, 1977. Indicate a primary or secondary Interest Area Code 13 or 14 on the Membership Records Questionnaire

Gastrointestinal
20(1): 5, 1977. Same as Cardiovascular

Nervous System
21(3): 25, 1978. Indicate a primary or secondary Interest Code 25 on the Membership Records Questionnaire

Renal Physiology
20(2): 17, 1977. Attend Renal Dinner at the Spring Meeting

Respiration Physiology
23(5): 6, 1980. Indicate a primary or secondary Interest Code 32 on the Membership Records Questionnaire

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SOCIETY NEWS

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Symposia Series on Career Opportunities in Physiology

The third in a series of symposia on career opportunities will be presented at the 1982 FASEB Spring Meeting in New Orleans. The symposium, titled "How to Get a Job in Physiology," is scheduled from 4:30 to 6:00 PM on Tuesday, April 20, 1982, in Ballroom C of the New Orleans Hilton.

This series of symposia is organized by The Career Opportunities Committee of APS as the result of a suggestion by one of the Sustaining Associate Members of the Society. The first symposium was held during the 1981 Spring Meeting and proved to be extremely popular in terms of both attendance and response. The second symposium was conducted at the APS Fall Meeting last October in Cincinnati and was equally well received.

The 1982 Spring Meeting symposium is being organized by David F. Bohr, who was the Society President when the APS Council first established the Committee. This session will open with a overview by Dr. Bohr and be followed by Billy Clement, the FASEB Placement Service Manager, who will describe that service. Walter C. Randall, the APS President-Elect and Chairman of The Career Opportunities Committee will then speak on the subject of the mentor's responsibility.

The symposium is open to all registrants at the 1982 FASEB Spring Meeting.

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

MEMBERSHIP RECORDS QUESTIONNAIRE

PLEASE MARK ALL ENTRIES IN RED.

CURRENT MAILING LABEL OR
PRINT NAME & ADDRESS

DATE _____

DATE OF BIRTH
Month Day Year

EMERITUS MEMBERS:
Check, if you would consider temporary or part time employment ☐

OPTIONAL PERSONAL DATA
SEX
☐ Female ☐ Male
A ☐ American Indian or Alaskan Native
B ☐ Asian or Pacific Islander
C ☐ Black
D ☐ White E ☐ Hispanic

POSITION TITLE CODE (SEE REVERSE) ☐

TYPE OF INSTITUTION Check one. (If retired, or unemployed check descriptors appropriate to last position held.)

MEDICAL SCHOOLS
33 _____ Physiology Departments
34 _____ Other Preclinical Departments
35 _____ Clinical
36 _____ Administration

OTHER
37 _____ Hospitals and Clinics
38 _____ Veterinary Schools
39 _____ Dental Schools
40 _____ Public Health and Graduate Schools
41 _____ College or University
42 _____ Commercial Companies
43 _____ Government (Inc. V.A.)
44 _____ Institutes and Foundations
45 _____ Private Practice
99 _____ Other (Specify)

EARNED DEGREE CODE (SEE REVERSE) NOT MORE THAN TWO ☐ ☐

MAJOR TYPE OF WORK (Check not more than one.)

04 _____ Research 05 _____ Teaching 06 _____ Administration 07 _____ Clinical

SECONDARY TYPE OF WORK (Check one only if it represents a significant portion of time and is different from your major type of work.)

04 _____ Research 05 _____ Teaching 06 _____ Administration 07 _____ Clinical

PRIMARY INTEREST AREA: (Enter the appropriate number from the list of interest area codes on the reverse also enter the letter under the area selected which best describes your specific interest.)

☐☐ MAJOR AREA ☐ SPECIFIC INTEREST

SECONDARY INTEREST AREA (If appropriate)

☐☐ MAJOR AREA ☐ SPECIFIC INTEREST

IF YOU HAVE SERVED ON A GROUP OR COMMITTEE WHICH IS ADVISORY TO THE GOVERNMENT CHECK AS APPROPRIATE.

A _____ Presidents Scientific Advisory
B _____ National Academy of Sciences
C _____ National Institutes of Health
D _____ Nat'l Aeronautical and Space
E _____ Dept. of Interior
F _____ Dept. of Defense (or Constituent Dept.)
G _____ Dept. of Agriculture
H _____ Congressional (Specify)

IF YOU HAVE EVER SERVED ON THE FOLLOWING APS GROUPS PLEASE CHECK AS APPROPRIATE.

A _____ Council
B _____ Education Committee
C _____ Finance Committee
D _____ Membership Committee
E _____ Program Committee
F _____ Publications Committee
G _____ Editorial Board (Specify)
H _____ Session Chairman
I _____ Symposia Speaker
J _____ Public Affairs
K _____ Public Information
L _____ Senior Physiologists
M _____ Porter Development
N _____ Animal Care & Experimentation
O _____ Committee on Committees
P _____ Centennial
Q _____ Financial Development
R _____ Career Opportunities in Phys.
S _____ Educational Materials Review Board

(OVER)

I AM A MEMBER OF THE FOLLOWING NATIONAL PROFESSIONAL SOCIETIES: Outside of FASEB:

A _____ American Association of Anatomists
B _____ American Institute of Biological Sciences
C _____ American Chemical Society
D _____ American Society for Cell Biology
E _____ American Society for Clinical Investigation
F _____ American Society of Mechanical Engineers
G _____ American Society of Microbiology
H _____ American Society for Neurochemistry
I _____ American Society of Plant Physiologsts
J _____ American Society of Zoologists (DCP&B)
K _____ Association of Chairmen of Departments of Physiology
L _____ Biomedical Engineering Society
M _____ Biophysical Society
N _____ Endocrine Society
O _____ Institute of Electrical and Electronic Engineers
P _____ Society of General Physiologists
Q _____ Society for Neuroscience
R _____ Canadian Phys. Society
S _____ American Medical Association
Z _____ Other (Specify)_____

POSITION TITLE CODES (use most closely related description)

A. Director or Deputy
B. Chairman
C. Professor
D. Research Associate
E. Sr. Research Associate
F. Associate Professor
G. Assistant Professor
H. Laboratory or Research Director
I. Institute Director
J. Dean or Associate Dean
K. Executive Secretary
L. Academician
M. Corresponding Academican
N. Private Practice or Consultant
0. Researcher
P. Medical Intern
Z. Other

EARNED DEGREE CODES

CODE	DESCRIPTION
01	PH.D. or Dr. Phil.
03	M.D. or Dr. Med.
05	D.V.M. or Dr. Vet.
06	ScD.
07	D.D.S., D. Odont or D.O.
10	ED.D or Dr. Ed.
25	Cand. Med.

INTEREST AREA CODES

01. Anesthesia

02. Anatomy and Embryology
A. Microscopic
B. General
C. Fetal physiology

03. Anthropology

04. Biochemistry
A. General
B. Clinical

05. Biophysics

06. Biomedical Engineering

07. Blood
A. General
B. Erythrocytes
C. Hematology
D. Cell formation
E. Volume
F. Coagulation
G. Platelets
H. Plasma proteins
I. Rheology

08. Cardiovascular
A. General
B. Heart
C. EKG
D. Cardiac output
E. Artificial heart
F. Coronary
G. Cardiac dynamics
H. Cardiology
I. Blood flow
J. Peripheral circulation
K. Hemodynamics
L. Hypertension
M. Blood pressure
N. Atherosclerosis
O. Hemorrhage
P. Blood capillaries
Q. Venous return
R. Shock
S. Pulmonary circulation
T. Splanchnic circulation
U. Control

09. Cellular and Tissue
A. Cytology
B. Mitochondria
C. Protoplasm
D. Cell membranes
E. Cell surface chemistry
F. Histochemistry
G. Electron microscopy
H. Tissue culture
I. Tissue metabolism
J. Tissue elasticity
K. Connective tissue

10. Comparative Physiology
A. General
B. Insects
C. Fish
D. Reptiles
E. Avian
F. Plants
G. Marine biology
H. Crustacean
I. Mammalian

11. Electrolytes and Water Balance
A. General
B. Active transport
C. Ion transport
D. Body fluids
E. Lymph
F. Salt and water balance

12. Endocrines
A. General
B. Neuroendocrines
C. Pituitary
D. Thyroid
E. Parathyroid
F. Insulin
G. Adrenal/Medulla
H. Adrenal cortex
I. Sex hormones

13. Energy Metabolism & Temperature Regulation
A. Energy metabolism
B. Calorimetry
C. Exercise
D. Fatigue
E. Temperature regulation

14. Environmental
A. Aviation
B. High Altitude
C. Space Medicine
D. Underwater
E. Bioclimatology
F. Hypothermia and cold
G. Hibernation
H. Shivering
I. Adaptation
J. Hyperthermia and heat
K. Sweating
L. Industrial health
M. Air pollution

15. Enzymes
A. General
B. Kenetics
C. Antienzymes
D. Digestive enzymes

16. Gastrointestinal
A. General
B. Deglutation
C. Gastric secretion
D. Gastric mucosa
E. Gastroenterology
F. Pancreatic juice
G. Absorption
H. Intestinal motility
I. Digestion
J. Gastrointestinal surgery
K. Salivary secretion
L. Intestinal secretion
M. Gastric Motility

17. General Physiology

18. Gerontology
A. Aging
B. Degenerative diseases
C. Geriatrics

19. Immunology

20. Liver and Bile

21. Lipids and Steroids
A. General
B. Fat metabolism
C. Cholesterol metabolism
D. Obesity
E. Fatty acids
F. Other (Specify)

22. Microbiology
A. General
B. Bacteria
C. Viruses
D. Yeasts
E. Cancer cells

23. Minerals, Bone and Teeth
A. General
B. Bone
C. Calcium metabolism
D. Calcification
E. Dental caries
F. Mineral metabolism

24. Muscle and Exercise
A. General
B. Muscle metabolism
C. Muscular contraction
D. Skeletal muscle
E. Heart muscle
F. Smooth muscle
G. Muscle cells
H. Muscle chemistry
I. Muscle enzymes
J. Muscle-physical processes

24. Muscle and Exercise (Cont'd)
K. Muscle-nerve
L. Exercise

25. Neurosciences
A. General
B. Brain
C. EEG
D. Cerebral cortex
E. Mid brain
F. Brain stem
G. Spinal cord
H. Autonomic regulation
I. Peripheral nerve
J. Nerve cells
K. Vision and optics
L. Hearing and acoustics
M. Taste
N. Speech
O. Other senses
P. Sleep
Q. Learning
R. Behavior
S. Conditioned responses
T. Comparative
U. Neurological diseases
V. Psychiatry
W. Psychology
X. Cerebellum
Y. Hypothalamus
Z. Pain
Reflexes

26. Nutrition and Food
A. General
B. Diet
C. Nutritional value of foods
D. Chemistry of foods
E. Vitamins
F. Digestion
G. Carbohydrate metabolism
H. Protein metabolism
I. Fat metabolism
J. Nutritional diseases

27. Pathology

28. Pharmacology
A. Pharmacodynamics
B. Evaluation of drugs
C. Autonomic drugs
D. Cardiac drugs
E. Anticonvulsant drugs
F. Analgesics
G. Toxicology
H. Therapeutics
I. Chemotherapy
J. Antibiotics
K. Neuropharmacology

29. Radiology
A. Radiobiology
B. Ionizing radiation
C. Ultra-violet
D. Thermal burns
E. Cosmic rays

30. Renal
A. General
B. Tubular
C. Urinary tract
D. Renal disease
E. Comparative
F. Diuretics
G. Artificial Kidney

31. Reproduction
A. Fertilization
B. Pregnancy
C. Fetal physiology
D. Lactation
E. Obstetrics & Gynecology

32. Respiration
A. Pulmonary physiology
B. Respiration mechanics
C. Pulmonary diffusion
D. O_2 and CO_2 transport
E. Tissue respiration
F. Anoxia
G. O_2 poisoning
H. Asphyxia
I. Respiratory diseases
J. Chest diseases
K. Hypercapnia
L. Artifical lungs
M. Resuscitation
N. Control

99. Other
Z. Other

News from Senior Physiologists

Ancel Keys to Edward Adolph:

We spend more time in Italy than in Minnesota these days. Much as we like Minnesota, in Italy we are closer to follow-up work on our epidemiological studies, the "Seven Countries Study," that started in 1958, and we enormously enjoy our year round gardening in the mild climate and gorgeous scenery of the Tyrrhenian coast of southern Italy. So we frequently shuttle back and forth across the Atlantic.

Inflation in Italy is worse than in the United States, and the cost of living is the first topic of conversation. Bread and wine are cheap, but the price of meat and fish is nearly double that in the States, and we pay $3 a gallon for gasoline. But food is a small item in our budget; we are now almost vegetarians, living year round on the produce of our garden, orchards, and vineyards. Of course we don't count the cost of our farmer-gardener, fertilizer, insecticides, and equipment. Happily, our property tax is very low, but there is an 18% sales tax on everything but food and clothes.

We are just back from Italy, a bit weary still from all the goings-on in connection with an international symposium in my honor on atherosclerosis and its prevention. Seventeen countries were represented at the three days of meetings at Anacapri, followed by a day's trip by chartered hydrofoil from Capri to Acciaroli, less than 3 miles from our home "Minnelea." Buses brought the crowd to Minnelea, where some went swimming in the sea below while others wandered in the gardens or simply relaxed, enjoying the view of mountains and sea.

At Minnela we provided cold drinks and nibbles before the buses carted everyone to the Hotel Velia a mile away to eat a great multi-course meal dominated by the catch of the local fishermen. Afterward, only the strongest took off with me for a hasty visit to the nearby excavations of Velia, the city founded by Greeks in 535 B.C. Velia, or "Elea," as it was once called, was the locus of the Eleatic School of philosophy and also seemingly some kind of medical center, quite possibly the forerunner of Salerno, credited with being the first medical school of Europe with a history going back more than a thousand years. In documents of the year 900 the School of Salerno was mentioned as "ancient."

Before the Anacapri meetings our house was full of guests for several weeks, and when the hydrofoil left after the visit to Minnelea we had new house guests from Japan, Spain, Germany, and the United States. Our good friends, the Jerry Stamlers of Chicago, also had house guests at their villa two hundred yards away, so it was a busy time until we left for the States, with a visit to Lisbon and old friends there on the way. We return to Italy in September in time to make the wine before driving to Lugano for another three-day symposium on atherosclerosis.

In 1980 I gave invitational lectures in California, Greece, Sweden, Italy, Argentina, Italy again, and Spain, all different, with manuscripts required for publication. When the Harvard Press published my book *Seven Countries* last year, I thought I'd be able to relax and spend more than a few hours a day in the gardens of Minnelea. But there are still masses of undigested data from the follow-up of the men we first enrolled in 1947 in Minnesota and the Seven Countries men we began examining in 1958. I recently received the final report and a pile of computer output on the status at the end of 1980 of the 900 men we examined in Finland in 1956.

So it is a problem to set priorities among the jobs of analysis and writing that compete for my time. Leading articles in the *Lancet* last September and this July took care of two items, but there are still five more demanding attention. In the meantime I keep in good health....

Our son Henry is Clinical Director of Radiation Oncology at the Strong Memorial. He was able to join the Anacapri affair and have a very short stay at Minnelea.

Laboratory of Physiological Hygiene
School of Public Health
University of Minnesota
Minneapolis, MN 55455

Douglas H.K. Lee to Edward:

I remain moderately busy; perhaps it is old age, perhaps the tropical environment, but things take longer to do than used to be the case. However, since we moved here five years ago I have managed to get published the asbestos book that I prepared with Irving Selikoff at Mt. Sinai (Academic Press). Two papers have appeared in *Environmental Research,* one on the historical aspects of the asbestos story and one on heat indices. Another on heat indices is in preparation. In 1979 I visited my family in Brisbane, Australia, and took in meetings of the Royal Australasian College of Physicians and of the Society of Occupational Medicine. The new university buildings are delightfully arranged, and the atmosphere seems in excellent accord with modern needs. I was able to reestablish contact with several former colleagues, notably R.K. Macpherson, now Professor Emeritus, School of Public Health and Tropical Medicine, University of Sydney. (We published a paper on Tropical fatigue and warfare in the first number of JAP.) The Queensland Institute of Medical Research, which I had a hand in establishing back in the 40's made me an Honorary Fellow, in conjunction with F.M. Burnet and others of international renown. So I have been going back over old ground.

Locally, in between bouts of fighting back the jungle, I have been monitoring construction of our new airport for possible environmental effects, and for a while took a mild interest in local "archeological" studies, but these have now largely lapsed. As we get older, we feel the need to be near good medical facilities and will probably move to Florida. Pharo Gagge and his wife were through here a short while back; they also are planning on moving to Florida before long. Requests for reprints still trickle in; this week there was even a request from Novosibirsk for a book.

Deer Hill Rd.
Nazareth 5-1, Star Rte.
St. Thomas, Virgin Is 00801

Joseph Holmes to Edward:

I am an Emeritus Professor and entered this status in 1977. At that time I was working primarily in diagnostic ultrasound since I had retired as Head of the Renal Division in 1972 and had given up my work in kidney disease, electrolytes, and renal function.

I had started work with ultrasound as an imaging technique back in 1950 in conjunction with Dr. Douglas Howry, one of the pioneers in this field. I was particularly interested in the technique because of my interest in fluid balance and the fact that this was the best of the imaging techniques for showing and depicting fluid within the body.

I have spent a great deal of time trying to collect data on the early days of diagnostic ultrasound and to write up the material for a variety of different purposes. We have also been hoping that we can get an exhibit through the efforts of the American Institute of Ultrasound in Medicine (AIUM), in one of the major museums in the country. Historical material of this type is always of interest to many, but old equipment that depicts this technique's progress is not of great interest because of space and storage problems. It ia amazing to me the general usage of diagnostic ultrasound as one looks back through the years of how long it took to convince others the importance of its medical applications. It has even reached the point of usage in doctors' offices in the areas of echocardiography and OB/GYN and ophthalmology.

My other major writing project is on the presentation of over 600 cases of polycystic kidney disease and examination of either patients or family members and how one might make a diagnosis in the early phases of the disease prior to childbearing and thus be in a position to offer genetic counseling. These data have been computer analyzed, and we are now getting ready to present it in written form.

We were over in Denmark in April to receive an honorary membership from the Danish Ultrasound Society. It was a pleasant trip and great fun.

I have been particularly interested in preserving old historical material in a field such as diagnostic ultrasound. This is always difficult, because I've discovered that reliance on the memory of those who worked with it 30 to 40 years ago is not always accurate. The material was collected selectively in relation to what an individual remembered. Much material was thrown out. However, it is fun to see the technique one worked on for years suddenly reach great importance in medicine.

University of Colorado Health Sciences Center
4200 E. Ninth Ave.
Denver, CO 80262

Samuel Pond to Edward:

I'm surely in the land of the living, even approaching 92. I keep on the move and in good or better health (retired and living in central Maine at Cobbosseecontee lakeshore).

Recently we were visited by the retiring Head of Purchasing at Eastman Kodak, a neighbor when I was at University of Pennsylvania Medical School. So we are in touch on an occasion or two with old friends. We were on Cape Cod recently (wedding of granddaughter).

We travel little but keep in touch with some local governmental matters (Town Committee on the Street-Lighting) and purification of our lake water supply (for recreation). For exercise I still have trees to fell and wood to prepare for next winter, as we heat, partially, by and old-fashioned kitchen stove. My wife and I participate in local church community affairs. Around home we will continue to tinker. At present I am putting together a few notes, sort of an autobiography: early work with General Electric, Stone & Webster, attending many of the early lectures at MIT, 1913-15, Boston, helping set up early X-ray technics at Rhode Island hospitals, and developing lab electronics with Rhode Island Board of Health, which initiated some retraining of physicians in TB and venereal disease by use of public health exhibits and needed my help with crude wireless transmission of public health lectures. Lots of fun in "them old days," but a good start in fundamental science.

I have a moderately good chance for carrying on a while longer. Friends and relatives help us all around. It's good to be alive in a rapidly and ... changing world.

East Winthrop, ME 04343

Isaac Starr to Edward:

My life was changed by the loss of my wife about 2 years ago, and after living alone in a big house for two years I gave up and moved to a retirement home. I boast of 4 children, 12 grandchildren, and 4½ great grandchildren at the last count. The move did not affect my work at the University.

The University of Pennsylvania has been very kind to me, and I continue to have laboratory space and a small office in the University Hospital. I have a part-time secretary. My research costs very little. I gave up my grant voluntarily many years ago and raise what I need myself. In recent years I have not acquired much new data but have spent my time studying the large body of data I acquired by testing normal persons and patients with heart disease during the last 25 years. Many of these have been observed for long periods of time. My data and my interest differs from the usual studies made by clinicians and physiologists in that I am a Newtonian and seek a solution of the problems of heart disease through the calculus, i.e., I am interested in the velocity and acceleration of the ejected blood and seek to detect cardiac strength and weakness, cardiac coordination and incordination, and the effect of treatment upon them by such measurements.

This large body of data has given me a lot to do, and I find that I am making more and more use of a big computer such as the IBM Unicol 360 to help me analyze it. Since I am presumed to have "retired" (at the age of 65) I have published 45 papers and have two more in press.

When I was a young man, the pathological viewpoint prevailed in clinical medicine. Now, the physiological viewpoint prevails and there is a tremendous lot to be done. One should not hesitate to advise young men to enter the field midway between physiology and clinical medicine.

Apt. D402, Cathedral Village
600 Cathedral Rd.
Philadelphia, PA 19127

Oscar Richards to Edward:

Your mention of our trip to the Growth Society came as I had just sent my old programs and pictures to the Society for their archives. I have very happy memories of those meetings with time to visit with friends and make new ones.

I retired from the American Optical Research Dept. in 1967. Three of the Optometry Colleges invited me to join them. As former Oregonians, my wife and I planned to return to Oregon. Pacific University not only gave me the most attractive offer but had the above advantage. I enjoyed teaching the Environmental Vision Course until 3 years ago. Now I give lectures on color vision and color measuring and have several seniors doing the required O.D. degree theses under my direction. I plan to retire again in another year.

When I came here, I continued as a consultant to American Optical Society for several years, and to do this I brought part of my laboratory equipment with me. The microscope equipment and my library are to go to the Smithsonian Institution. I am now working toward catching up with my unpublished backlog. A paper on the early 19th Century microscopes of the Spencers is awaiting publication. In 1971 I received the Prentice Medal from the American Academy of Optometry, a delightful and unexpected honor.

College of Optometry
Pacific University
Forest Grove, OR 97116

Chandler Brooks to Horace Davenport:

I am well and busy with one or another of my occupations. As Editor-in-Chief of the *Journal of the Autonomic Nervous System*, I take a rather personal interest in ultimately reading all the papers. I spend quite a bit of time converting language use into what I consider correct and comprehensible English. I think the Journal will succeed, and papers are now coming in faster than they can be published. There is a pleasing diversity of subjects, countries, and authors. One of our policies is to publish symposia—at least one or two a year if they are small. This fast publication is preferable to the two-or three-year delay in producing the usual loosely constructed books. We have our difficulties—among them is excluding materials published before; this is hard on hosts who invite or are compelled to invite eager symposium participants who believe they can thus publish something referees would not normally approve. However, I think we are going to succeed in reproducing some interesting symposia of high quality. It is work and occasionally quite boring, but I do want to say two things which make me proud to be a member of the international community of scientists.

First, authors are very appreciative of editorial and referee help, and most persons trust our good intentions. Second, our scientists are very willing to help us by refereeing papers. They spend hours, and many do an extremely thorough and thoughtful job. I have to call on many from various countries and fields of knowledge because interests in autonomic system function involve all fields of physiology.

My second occupation is as Chairman of the Grants Committee of a small foundation. Our concept is to help people in other countries solve their problems and build a better life in their own homeland. Bringing refugees hare is no solution in our opinion. We also seek to foster projects that will be self-sustaining. People need food, medical service, education, a viable social organization, economic attainment, and aid to cultural preservation and development. That is our order of priorities.

I still do a bit of teaching in my school and some lecturing elsewhere: Sao Paulo at the Latin American Physiological Congress, Japan, Korea, Taiwan, South Africa, and Kiev. I do a bit of research with adequate modern ideas but antiquated equipment. I publish experimentally obtained data as well as the "fruit of the mind." Finally I labor slowly in the field of History and Philosophy of Medical Sciences and consider the history and the bases for ethical developments....

I am working at many things, and I presume I will not finish them all. Age does not kill curiosity or activity of the mind; it brings a new freedom but also new anxieties.

Dowstate Medical Center
State University of New York
Brooklyn, NY 11203

Ruth Conklin to Horace:

I was interested to know that Louise Marshall has taken on the chairmanship of the Senior Physiologists Committee. She will be good at it as she is at everything she does.

My life continues to be full and active, though I'm afraid not filled with research or writing. I have recently had for three weeks three young male Vietnamese refugees (boat people) as my guests and have enjoyed them very much. They are now settled in an apartment with an older relative, who has been here a year and a half and has been employed. I am impressed with the caliber of the Vietnamese people I have known. They are fine people, hard working, conscientious, and anxious to be on their own. Communication is a barrier, of course, but they are eager to learn English and work hard at it. After their unspeakable treatment in escaping and holdups by pirates on the boat, they appreciate greatly a decent and sympathetic attitude.

155 College Ave.
Poughkeepsie, NY 12603

Jonathan Rhoads to Horace:

I am still practicing surgery, though the number of patients I take care of is considerably smaller than it was 10 and 20 years ago. I am editing the Journal *Cancer*, which takes considerable time even though we rely on experts in many fields to review the 1,800 papers a year that are being submitted. I have been serving the last two to three years with the General Motors Cancer Research Foundation as Chairman of the Awards Committee to help conduct the search for appropriate candidates for the three $100,000 awards the Foundation gives, one in basic science, one in diagnosis or treatment, and one in prevention. The third major extracurricular activity has been the American Philosophical Society, which did me the great honor to elect me President. This involves attending a remarkably large

number of committee meetings as well as a two-day meeting in the fall and a three-day meeting in the spring.

I am continuing to do some writing for scientific journals. I am afraid this is more in the field of history, background, memoirs, etc. than any real additions to knowledge, but it nevertheless takes quite a bit of time. My scientific activities are also more in the field of preparing teaching materials for occasional visiting professorships, and I have not been doing any experimental surgery or work at the bench for the last several years.

Probably my greatest satisfactions have come from the success of intravenous hyperalimentation. My colleagues deserve the credit for this, but they very generously include me often because of my insistence that we explore the positive side of nitrogen balance as achieved by the intravenous route. The clinical results were unexpectedly (to me) positive, so that this has become a recognized part of postoperative care in the treatment of a number of surgical and some pediatric, medical, and psychiatric problems.

Hospital of the University of Pennsylvania
3400 Spruce St./G1
Philadelphia, PA 19104

Rachmiel Levine to Horace:

From 1936 to 1960, I pursued my work at Michael Reese Hospital, Chicago, and held a teaching position in the Department of Physiology, University of Chicago. From 1960 to 1970, I assumed the Professorship of Medicine at New York Medical College. In November of 1970, I came to California to assume the Medical Directorship of the City of Hope Medical Center. Simultaneously, I directed the Department of Metabolism and Endocrinology.

In July 1981, I go on emeritus status. I will retain office space and secretarial support and will devote my time to writing and general counsel to staff and Board of the institution—upon request, without a mandate. Summers, at Woods Hole, as usual.

On the occasion of my 70th birthday (fall of 1980), a Symposium on Diabetes was held at Rancho Mirage (Palm Springs area), and it has been published in *Diabetes Care*. I am finishing a review on insulin action for *Vitamins and Hormones*. My interests remain strongly the same. I only wish I was at an age to learn the requisite new techniques in the field of hormone action and contribute to data, but that is a futile wish. I can, however, continue to enjoy the field, kibitz the active players, and encourage some of them. I hope I can do this without becoming a nuisance.

The leading health indicators (blood pressure, lipids, blood sugar, ECG, respiratory capacity, creatinine, etc.) are in good shape. I miss the old facility of recalling the volume and page of a particular reference. Index cards have become a necessity, but it is difficult to remember where the index cards are!!

City of Hope National Medical Center
1500 E. Duarte Rd.
Duarte, CA 91010

Future Meetings

1982	
APS Fall Meeting	Oct 10-15, San Diego
1983	
FASEB Annual Meeting	Apr 10-15, Chicago
APS "Fall" Meeting	Aug 21-25, Honolulu
IUPS Congress	Aug 28-Sep 13, Sydney
1984	
FASEB Annual Meeting	Apr 1-6, St. Louis
*APS "Fall" Meeting	Jul 29-Aug 7, Lexington
1985	
FASEB Annual meeting	Apr 21-26, Anaheim
*APS "Fall" Meeting	Aug 4-9, Buffalo

*Campus meeting

George Thorn to Horace:

I was delighted to receive your letter and will give you brief resume of my professional activities since retiring from the Peter Bent Brigham as Physician-in-Chief and from Harvard Medical as Hersey Professor of the Theory and Practice of Physics in 1972.

I continued as Editor-in-Chief of Harrison's *Principles of Internal Medicine* in its 8th edition and with that completed my 30 years of editorship with this textbook. Prior to retirement from the Brigham I was honored by being made a Corporation member and later elected as a life member and a member of the Executive Committee, its governing body, at the Massachusetts Institute of Technology, where I have now served for 11 years through the inauguration of two presidents. My main activity is the continuation of my association with the Howard Hughes Medical Institute, where I am Chairman of the Medical Advisory Board and a member of the Executive Committee. We have an outstanding group of Investigators who are leaders in their field and are located in 12 medical school areas in the country and involved in research in the areas of genetics, immunology, and metabolic regulation. In addition, I am associated with two foundations—the Health Sciences Fund, which supports graduate students at MIT, young faculty members at MIT, and faculty members at the Harvard and Boston University Medical Centers who collaborate with someone at MIT and are involved in biomedical engineering research. I am Vice President of this Fund. With the death of Uncas Whitaker a few years ago, the Whitaker Foundation was established, and I was asked to chair the scientific review board. This Foundation makes grants in the field of biomedical engineering to universities in the eastern half of the United States. This is a very active program and, again, one which seeks to strengthen the relationship between the technical knowledge of engineering with biomedical scientists.

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Metabolic Regulation of Coronary Blood Flow

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A change in blood flow rate and/or O_2 extraction are the two mechanisms which adjust O_2 delivery to meet organ work. In most organs both mechanisms contribute more or less equally. The heart and kidney, however represent extremes in which one of the two mechanisms predominates. Basal coronary resistance is very high, the resultant of autoregulation (myogenic?) and perhaps α-adrenergic vasoconstriction (19), though the importance of neurally mediated vasoconstriction has recently been questioned (9). There is no evidence that the heart produces vasoconstrictor metabolites which contribute to basal resistance. As a consequence of this high basal tone and a high rate of O_2 usage, myocardial O_2 extraction is very high, 65-80%. Indeed, basal O_2 extraction is higher in the heart than in any other organ. Because extraction is already very high, the coronary circulation adjusts O_2 delivery primarily, though not exclusively, by changing flow. The coronary circulation has a large vasodilator reserve; maximum coronary flow rates may exceed basal levels by as much as 600%. By contrast, renal vascular resistance is low, only about 20% that of coronary resistance, and vasodilatory capacity is negligible. Renal O_2 extraction is normally low, 2-4 ml O_2/dl; a change in O_2 extraction is the major response to a change in renal O_2 demand.

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Current thinking holds that cardiac metabolism is the dominant factor in coronary blood flow regulation. Physical factors such as blood pressure and the compressive forces exerted by working myocardium clearly influence coronary flow, as do reflexes. However, the moment-to-moment adjustments in coronary flow to meet changes in cardiac effort are essentially metabolic. This view is the product of many experiments which show a strong correlation between coronary flow rate and cardiac effort, measured either by myocardial work or O_2 usage.

Metabolic flow regulation is, in essence, the resultant of metabolic vasodilation superimposed on nonmetabolic vasoconstriction. The metabolic flow regulation hypothesis in its most general form proposes that coronary vasodilation is the direct result of a chemical consequence of heart cell activity. This chemical event could be the elaboration of a vasodilatory metabolite or, alternatively, the consumption of a metabolite that maintains coronary arterial tone.

The analysis which follows judges the candidacy of the metabolites that at one time or another have been proposed to be physiological regulators of coronary flow. This analysis employs some of the criteria recently proposed by Berne (1), supplemented by the additional requirement that the receptor or chemical process which initiates coronary relaxation should be known (Table 1).

Table 1
Properties of a Coronary Vasoregulatory Metabolite

Cardiac Effort	O_2 Usage ←	Cardiac Effort
↓		↓
O_2 Usage		Metabolite
↓		↓
Metabolite		Coronary Tone
↓		
Coronary Tone		
CAUSAL		COINCIDENTAL

1. The heart must generate the endogenous mediator.
2. Production must be coupled to cardiac effort.
3. The vasoactivity of the metabolite must be commensurate with its physiological concentration.
4. There must be a unique quantitative relationship between the interstitial fluid concentration of mediator and coronary resistance.
5. The coronary receptor (or mechanism of relaxation) must be known.

These criteria serve a very important purpose, that of minimizing the chance of mistaking coincidence for causality, a task which sometimes can be very difficult. However, we believe that the rigorous quantitative application of these criteria is essential, for this offers the best chance for correctly identifying the mechanism of coronary flow regulation. The relationship between cardiac effort, cardiac O_2 usage, and coronary flow rate illustrates this point. The problem here is to discriminate between two possible relationships (Fig. 1). As mentioned above, cardiac effort, O_2 usage, and coronary flow are strongly covariant. If these variables are causally related, their relationship will be strictly proportional and unique; i.e., this proportionality will be independent of the particular experimental conditions. In the case of cardiac effort and O_2 utilization, this is not so, because the amount of O_2 needed to support cardiac work varies according to the substrate being oxidized. Free fatty acids are the primary energy source for the heart. The oxidation of a representative acid, oleic, requires 52.2 ml O_2/kJ energy released. When glucose is the substrate, the O_2 requirement is 43.5 ml O_2/kJ, a reduction of 17%. Thus there is not a unique relationship between cardiac effort and O_2 usage.

The strong correlation between O_2 usage and coronary flow rate suggests that these variables may also be causally related. This idea importantly influences thinking about metabolic control of the coronary circulation. If it is true, the production of the metabolite that mediates flow must be uniquely related to O_2 usage. Two reasons argue against this. First, coronary flow can be proportional to O_2 utilization only if myocardial O_2 extraction is invariant. Although the transcoronary arteriovenous O_2 difference usually varies over a small range, it nevertheless *does* vary. This means that the relationship between coronary flow and O_2 usage cannot be strictly proportional under all conditions. Second, the experimental evidence that supports the dependence of coronary flow on O_2 usage is in reality an example of a spurious correlation. This is traceable to the fact that O_2 consumption is customarily estimated indirectly by calculation if the product of coronary flow rate and the arteriovenous O_2 difference. The hypothesis that coronary flow rate is proportional to O_2 consumption is tested by examining the regression of one variable on the other, which in actuality test the regression of coronary flow on itself. In modeling coronary circulatory control, it therefore, seems necessary, if not incorrect, to postulate that the production of a vasoregulatory metabolite is directly related to O_2 consumption. Indeed, it is equally possible that cardiac effort itself, perhaps a step in the sequence of excitation-contraction coupling, regulates release of the vasodilator metabolite.

Coronary Vasoregulatory Metabolites

Oxygen

The hypothesis that O_2 acts directly on coronary vascular smooth muscle proposes that as O_2 consumption rises, O_2 tension (P_{O_2}) in the vicinity of the coronary resistance vessels falls, causing these vessels to relax. If one considers that the disappearance of O_2 is the negative equivalent of the appearance of a metabolite, O_2 meets the first criterion for a vasoregulatory metabolite. However, it fails every other test. As just pointed out, there is not a unique relationship between O_2 usage and cardiac effort. In addition, we are not aware of any comparisons of coronary flow with direct estimates of interstitial P_{O_2}. However, isolated coronary microvessels maintain tone until P_{O_2} is $\leq$ 5 mmHg (12), which is well below the typical coronary venous P_{O_2} of about 20 mmHg. This does not support the idea that P_{O_2} changes within the physiological range might control coronary flow. The logical O_2-binding moiety to serve as an O_2 receptor is cytochrome aa_3. However, Coburn et al. (10) have shown that poisoning this enzyme with cyanide does not relax vascular smooth muscle to the same extent as lowering P_{O_2}. Thus the "receptor" which might mediate hypoxic coronary relaxation in isolated muscle experiments is unknown.

Carbon Dioxide

Since cardiac muscle is for all intents and purposes an "obligate aerobe," CO_2 is produced continuously as a consequence of oxygen usage in a proportion defined by the respiratory quotient. Case et al. (8) have demonstrated that changes in arterial CO_2 tension (P_{CO_2}) produce concordant changes in coronary venous P_{CO_2} and inverse changes in coronary vascular resistance. That myocardial P_{CO_2} estimated with microelectrodes corresponds closely to coronary venous P_{CO_2} (7) tends to validate inferences about the relationship between coronary resistance and interstitial P_{CO_2}. Raising arterial P_{CO_2} also intensifies the reactive hyperemic responses to coronary occlusions (26, 33).

However, the experimental support for the CO_2 hypothesis is incomplete. Just as in the case of O_2 usage, CO_2 production is not uniquely related to cardiac effort. The oxidation of oleic acid to support cardiac work yields 36 ml CO_2/kJ. Substituting glucose for oleate should raise CO_2 production per work equivalent by 21% to a value of 43.5 ml CO_2/kJ. Additionally, the evidence supporting the candidacy of CO_2 comes primarily from experiments in which tissues P_{CO_2} was manipulated by modifying the P_{CO_2} of either systemic or local coronary arterial blood. Except for measurements of tissue P_{CO_2} during coronary occlusion (6), there is no information on how the interstitial concentration of endogenous CO_2 changes during physiological responses or whether there is a quantitative relationship between coronary flow and interstitial P_{CO_2} under these conditions. Work to date has neither identified a CO_2 receptor nor provided an alternative explanation of how CO_2 might regulate coronary resistance.

Hydrogen Ion

Heart muscle continuously generates CO_2 and organic acids, both of which could serve as sources of H^+. Concomitant changes in P_{CO_2} bedevil attempts to obtain unambiguous evidence for a primary role of H^+ in coronary flow regulation. The administration of fixed acids may increase (17) or decrease (14) coronary flow. Increases in cardiac work decrease coronary venous pH (39), but as yet no one has demonstrated a quantitative relationship between cardiac effort, interstitial pH, and coronary blood flow. How H^+ might initiate coronary relaxation is unknown.

Potassium

The observation that K^+ extrusion during repolarization varies directly with the level of myoplasmic Ca^{2+} (20) supports the possibility that the release of K^+ is coupled to cardiac effort. Evidence implicating K^+ in coronary vasoregulation points more to a facilitative rather than a determinative role. Coronary venous [K^+] changes in response to pacing tachycardia precede the associated changes in coronary resistance (28) as predicted by the K^+ hypothesis. However, K^+ release soon abates even though flow remains elevated. Conversely, K^+ infusions at rates sufficient to raise interstitial [K^+] to the levels calculated to obtain during pacing do not increase coronary flow to levels commensurate with pacing. Other studies confirm the evanescent effect of K^+ on coronary flow (5). Ouabain antagonizes the coronary vasodilatory effect of K^+, suggesting the Na^+-K^+- ATPase is the coronary K^+ receptor (5,29).

Tricarboxylic Acid Cycle Intermediates

Intracoronary administration of Na acetate or Na citrate (27) or Intravenous tris (hydroxymethyl) aminomethane acetate (23) cause dose-dependent coronary vasodilation, which suggests that the release of glycolytic and tricarboxylic acid cycle intermediates could regulate coronary flow. However, those observations constitute the only support for this hypothesis. In these experiments the anion concentrations necessary to produce these results were in the millimolar range. Whether the endogenous metabolite concentrations in the cardiac interstitium reach such levels or whether coronary resistance is proportional to these concentrations under physiological conditions is unknown. Neither vascular receptors for these anions nor an alternative explanation for coronary vasodilation is available. Thus there is little reason at this time to believe that these acids play a significant role in coronary vasoregulation.

Prostaglandins

The main support for the hypothesis that prostaglandins mediate coronary flow is the observation that intracoronary infusions of the prostaglandin precursor arachidonic acid causes coronary vasodilation and that cyclooxygenase inhibitors block this effect (16,18). Coronary microvessels contain the enzymes needed for prostaglandin synthesis (13). This and the recovery of prostaglandins from coronary venous blood (3) document local production. However, pharmacological inhibition of prostaglandin synthesis has no effect on the coronary vasodilation consequent to transient ischemia or hypoxia (18,32), suggesting that the vasoregulatory effects of prostaglandins may only be important in well-perfused myocardium. Prostaglandin I_2 (PGI_2) is a very powerful vasodilator, active in the nanomolar range, and is the likeliest candidate for a vasoregulatory prostaglandin. Its presence in minute amounts and its lability are important obstacles to establishing its role in coronary blood flow regulation. Thus we can find no reports of PGI_2 concentration in heart muscle or comparisons of rates of prostaglandin synthesis with coronary flow or indices of cardiac effort. The extremely high potency of PGI_2 suggests the presence of a specific coronary receptor, but definite information on this point is lacking.

Osmolarity

Hypersmolarity may cause vasodilation in skeletal muscle; the exuberant hyperemia that follows the intracoronary injection of radiographic contrast media suggests that osmolarity could also contribute to coronary vasoregulation. However, the limited information bearing on this question offers little support for this hypothesis. Active coronary hyperemia does not change the osmolarity of coronary venous plasma (39), nor will reducing plasma osmolality by hemodialysis affect coronary resistance (4). However, coronary venous colloid osmotic pressure rises by as much as 0.5 mmHg during reactive hyperemia (21). The latter does not relate changes in osmotic pressure to coronary flow, so it is difficult to judge the significance if this observation. How hyperosmolarity initiated coronary vasodilation is unknown.

Adenosine

Adenosine has long been known as a very powerful coronary vasodilator; its candidacy as a physiological regulator of coronary flow has been the subject of intense scrutiny over the past 20 years. The work of Berne, Gerlach, and their colleagues show that adenosine meets many of the criteria for such a regulator. Heart muscle produces adenosine continuously (34). Even though there are no techniques that precisely estimate interstitial adenosine concentration, evidence from intracoronary adenosine infusions in isolated guinea pig hearts (37) and from conscious dogs (30) indicates that the concentrations of endogenous adenosine which probably obtain in the interstitial space can account for the full range of coronary vasomotion. Directionally similiar changes of the adenosine concentration in pericardial superfusates, coronary flow, and indices of O_2 usage in conscious dogs suggest that adenosine may couple coronary flow to cardiac effort under physiological conditions (40). However, the fact that O_2 consumption is not strictly proportional to cardiac efforts weakens this evidence. Moreover, two other laboratories report that raising O_2 consumption by β-adrenergic activation stimulates adenosine production to a greater extent than raising O_2 consumption to the same degree by electrical pacing (25,35). The fact that theophylline blocks the coronary vasoactivity of exogenous adenosine but incompletely blocks reactive hyperemia has been an important challenge to the adenosine hypthesis (2). Whether this observation is a valid test of the hypothesis depends on whether adenosine alone supports the vasodilation of reactive hyperemia. Recent evidence suggests that this is not so. The destruction of endogenous adenosine by intracoronary infusions of adenosine deaminase catalytic subunits reduces reactive hyperemia by at most only one-third, and the combination of adenosine deaminase infusion and adenosine receptor blockade with theophylline does not further reduce the response (36). This experiment shows that adenosine contributes to postischemic vasodilation, but that other, unidentified, factors are collectively more important.

5'-Nucleotidase, an enzyme located on the surface of the cardiac cell, is thought to catalyze adenosine formation in heart muscle. How its activity is coupled to cardiac effort is unknown. Over 90% of the cardiac

adenosine pool is in an intracellular compartment and thus does not participate directly in coronary vasomotion (31). This greatly complicates estimates of the size of the interstitial compartments. Consequently, it is not known whether there is a quantitative relationship between coronary resistance and interstitial adenosine concentration. The pattern of the coronary vasodilator potency of adenosine analogs (30) supports the notion of a specific receptor and is similiar to the pattern of ligand specificity of adenylate cyclase-associated R_a receptors (24). Further support comes from studies on isolated coronary vessels and coronary membranes, which show concentration-dependent stimulation of adenylate cyclase by adenosine (22). An alternative hypothesis, that adenosine initiates coronary relaxation by blocking the pentration of Ca^{2+} into the coronary myocyte, is supported by electrophysiological studies demonstrating that adenosine blocks the slow inward current of the action potential of atrial muscle (38) and of vascular myocytes (15). ^{45}Ca flux studies on cultured rat aorta smooth muscle cells show that adenosine blocks Ca^{2+} ingress but not egress (11).

Summary

Current thinking favors the hypothesis that vasodilatory metabolites released from working heart cells adjust coronary flow to cardiac effort. Available evidence does not conclusively identify the metabolite responsible for this control but fairly well excludes primary roles for O_2 and glycolytic or tricarboxylic acid cycle intermediates. CO_2 (or H^+) and K^+ satisfy several of the criteria for a flow mediator, but neither seems sufficiently powerful to account for the physiological range of coronary vasomotion. The experimental evidence concerning prostaglandins is too scanty to either favor or reject their candidacy. A great deal of evidence favors the hypothesis that adenosine controls coronary resistance, but crucial elements of the proof of this hypothesis are either lacking or contradictory. It is possible that CO_2 (or H^+), K^+, and adenosine may act in concert to effect coronary vasomotor control.

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Tubular Reabsorption of Low Molecular Weight Proteins

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As long ago as 1836, Bright (4) recognized the relationship between albuminuria and kidney disease. It was only in relatively recent years, however, that the significance of low molecular weight proteinuria began to be appreciated (5). Whereas appearance of plasma albumin in urine reflects glomerular changes, increased excretion of the more readily filterable low molecular weight proteins (LM) is more likely to result from interference with their normal tubular reabsorption. This conclusion, of course, is justified only if the tubular absorption mechanisms have not simply become saturated because of a large increase in the filtered load of LM.

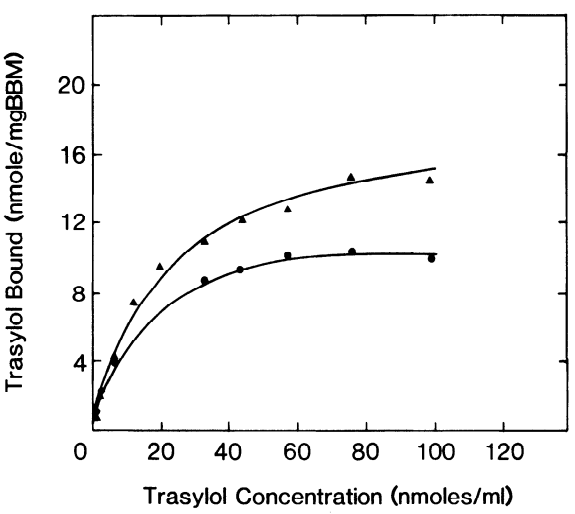
The association of low molecular weight proteinuria with proximal tubular damage is now well documented. Thus, exposure to cadmium (Cd) leads to increased excretion of β_2-microglobulin and other LM in urine (27). Another instance in which infliction of proximal tubular lesions leads to rejection of filtered LM is the increased excretion of lysozyme following treatment with nephrotoxic aminoglycosides in humans (22) and rats (8). Lysozyme is a cationic protein of molecular weight 14,000; like other classes of LM, it is readily filtered at the glomerulus (sieving coefficient 0.8, see Ref. 18). Inasmuch as aminoglycosides do not raise the filtered load of lysozyme, lysozymuria can be attributed to effects of the poisons on tubular reabsorption. The Fanconi syndrome, in which proximal tubular malfunction often is accompanied by increased LM excretion (11,13), provides a third example of tubular proteinuria.

Numerous other instances have been listed of tubular damage associated with LM excretion (26). Micropuncture and other experiments have confirmed that the site of LM absorption is the proximal tubule (see e.g., Ref. 7). The recognition that the proximal tubule normally absorbs large amounts of filtered protein and that low molecular weight proteinuria is of tubular rather than glomerular origin has led to considerable interest in the mechanism of tubular handling of LM. This paper will review our present understanding of this process. The inverse process, i.e., that of tubular secretion of LM, will not be considered here, although its occurrence has repeatedly been suggested (28).

The first step in absorption is the recognition of LM by, and their binding to, the brush border membranes. Details of this interaction have been investigated in several laboratories (2, 14, 30). Just and Habermann (14) worked with the Kunitz protease inhibitor (Trasylol), a cationic peptide with high affinity for the kidney. Isolated brush border membranes (BBM) from the rat renal cortex were found to bind Trasylol to a maximum extent of about 40 nmol/mg BBM protein (see Fig. 1); evidence was obtained for presence of more than one class of binding sites. One of the important determinants of Trasylol binding is the electrostatic interaction between BBM and substrate. Thus, as further illustrated in Fig. 1, reduction of the negative charge of BBM by removal of sialic acid with sialidase reduced the capacity of the membranes to bind the positively charged Trasylol. Reduction of the net positive charge on Trasylol by formation of the tetramaleoyl derivative (pI about 7) completely abolished the binding, whereas reaction with guanidine did not interfere. Similar findings were made also by Pesce et al. (25), who reported that binding of albumin and derivatives of varying isoelectric points to BBM from rabbit kidney varied with both the pI of the protein and the pH of the solution (see Table 1). Beyer et al. (2) reported that basic amino acids inhibit binding of the cationic LM lysozyme to BBM. Electric charge is clearly an important factor determining the reaction of proteins with BBM; it is not, however, the only factor. This follows from the observation by Just and Habermann that unlike Trasylol, the cationic peptide bradykinin is bound to BBM only to a small extent.

The work of Selenke and Foulkes (30) had as its primary objective to determine whether saturability,

Figure 1



Binding of Trasylol to brush border membrane (BBM) (modified from Ref. 14). ▲, Control BBM; ●, BBM treated with sialidase.

Tutorial Lecture, Fall Meeting of the American Physiological Society, 1981.

Table 1

Binding of Modified Albumins to BBM
(Modified from Ref. 26)

Albumin pI		4.9	5.5	6.5	8.5
		μg ^{131}I-Albumin Bound/mg BBM Protein			
Buffer pH	7.0	0.5	0.5	1.3	3.6
	6.5	1.0	1.6	2.1	7.0

Albumin, modified by reaction with ethylenediamine and a water-soluble carbodiimide, was incubated with brush border membranes (BBM) suspended in buffered mannitol-saline as described in Ref. 29 for 3 min.

Table 2

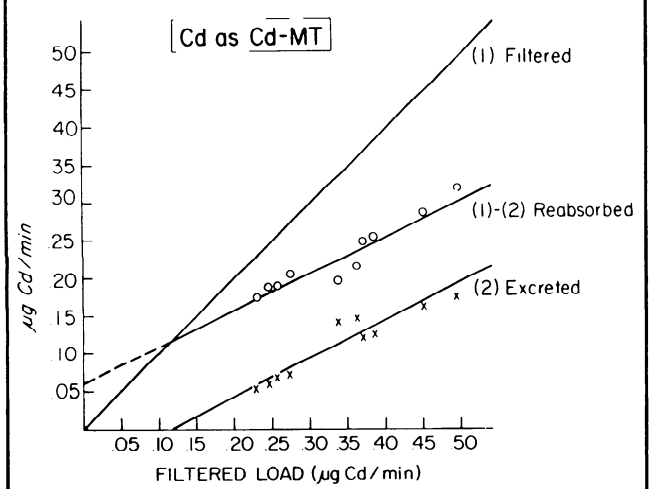
Reabsorption of Cd-Metallothionein in Rabbits
(Modified from Ref. 9)

	n	Fractional Reabsorption, %
A. Saturability		
Control (50 μg CdMT)	5	53 ± 16
+ 1,000 μ CdMT	5	8 ± 10
B. Sensitivity to myoglobin and Cd poisoning		
Control (100 μg CdMT)	5	42 ± 10
+ (3-10) mg myoglobin	5	15 ± 11
Cd-poisoned animals	4	3 ± 4

CdMT was injected intraarterially in a bolus containing 50 or 100 μg of ^{109}Cd-metallothionein (CdMT), together with [^{3}H]inulin and other additions as shown. Fractional reabsorption, shown as means ± SD of *n* experiments, was calculated from the isotope ratios in bolus and in urine.

specificity, and other characteristics of the tubular reabsorption of a low molecular weight protein (cadmium metallothionein, CdMT) in vivo resemble those of the binding of this protein to BBM in vitro. Such a similarity would suggest that the reaction at the membrane constitutes the rate and specificity-determining step in absorption. Metallothioneins are well-characterized proteins of molecular weight around 6,000 and isoelectric point around 4 (24); at physiological pH in plasma and glomerular filtrate CdMT is present therefore as anion. Nomiyama and Foulkes (23) had observed that tubular reabosorption of CdMT is mediated by at least two separate processes, one of which becomes saturated at relatively low levels of the protein in plasma (Fig. 2). When arterial boluses containing varying amounts of CdMT were injected intra-arterially into rabbits, recoveries of CdMT in urine approached those of inulin at high concentrations of CdMT (Table 2*A*). The fact that at sufficiently high plasma levels the clearance of CdMT approaches that of inulin implies that the protein is freely filterable at the glomerulus and that its reabsorption is wholly saturable at sufficiently high filtered loads. The reabsorption is depressed in animals previously poisoned with Cd or in presence of another anionic protein such as myoglobin (Table 2*B*). The inhibition of CdMT transport by myoglobin was subsequently found to be mirrored by CdMT inhibition of myoglobin reabsorption (10); no inhibition was exerted by the cationic LM lysozyme. In other words, myoglobin and CdMT appear to compete for absorption of a common charge-specific site. This conclusion recalls the similar inference drawn by Just and Habermann (14) about the binding of cationinc peptides to BBM.

Figure 2

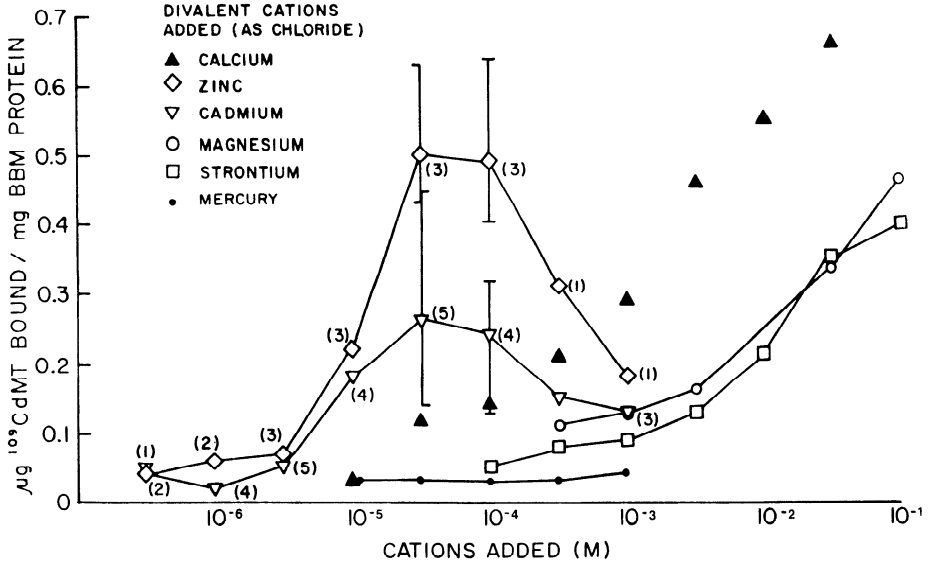


Renal reabsorption of Cadmium metallothionein (CdMT) (from Ref. 23).

A difficulty to be overcome before the reaction of CdMT with BBM could be studied in vitro arose from the fact that under the conditions employed by Just and Habermann, little binding of CdMT could be observed. Just and Habermann had already reported that anionic polypeptides like insulin or crotapothin are bound to BBM to a much smaller extent that the cationic Trasylol or not at all. These measurements were made with BBM suspensions in sucrose buffered to pH 7.6 with 0.01 M triethanolamine. Selenke (29) observed, however, that BBM (rabbit) readily binds the anionic CdMT in presence of such divalent cations as Ca and Zn; this phenomenon is illustrated in Fig. 3 and is presumably also explained by electrostatic interactions. The finding made it possible to study binding of CdMT to BBM in vitro and to compare the reaction with that in vivo. Details of the results were published by Selenke and Foulkes (30). Two classes of binding sites appear to be involved in this binding, recalling the two processes mediating CdMT reabsorption (23); the two processes are distinguished in vivo and in vitro on the basis of their saturability at low CdMT levels. Similarly to its action on CdMT absorption in vivo (10), myoglobin inhibits binding of CdMT to BBM, whereas lysozyme is ineffective (29); this is illustrated in Fig. 4. Both in vivo and in vitro, therefore, charge-specific sites appear responsible for reactions of CdMT with tubules. Finally, poisoning of rabbits with Cd inhibits both CdMT reabsorption in vivo and its binding to BBM in vitro.

Reaction of CdMT with BBM in vitro thus resembles closely that predicted from the characteristics of its handling by the tubule in vivo. The experiments with isolated brush border membranes may therefore be summarized by the conclusion that absorption of LM involves as its first step charge-specific interaction with a limited number of membrane sites. This conclusion readily accounts for further results on renal handling of LM in vivo. Thus, Cojocel et al. (7) measured renal uptake of intravenously injected lysozyme: this is depressed by cationic LM (cytochrome *c*, ribonuclease) and other basic compounds; myoglobin is ineffective. In

Figure 3



Role of cations in the binding of cadmium metallothionein (CdMT) to brush border membrane (BBM) (from Ref. 29).

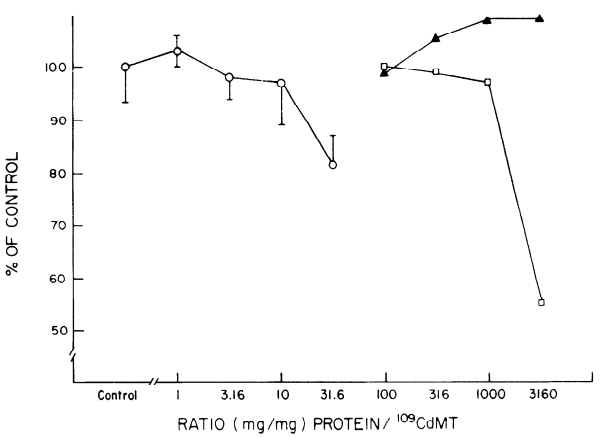
microperfusion studies absorption of ^{131}I-lysozyme was inhibited in a dose-dependent manner by cytochrome *c*. Similar findings have also been made by Sumpio and Maack (31), who reported that lysozyme competes with cytochrome *c* for renal absorption; no competition was observed between the cationic proteins and β_2-microglobulin (pI 5.4-5.7, see Ref. 26) or growth hormone. The reported arginine stimulation of urinary β_2-microglobulin excretion (21) cannot, however, be explained on such a basis: other factors, such as diuretic effects of arginine or its direct reaction with the anionic LM, may here be involved.

As in the case of higher molecular weight proteins (19, 20), tubular absorption of LM involves invagination of cell membranes with formation of endocytic vacuoles 3,6). This represents the second step in the reabsorptive process: LM first become associated with endocytic vacuoles and are subsequently transferred to lysosomes, as previoulsy described for albumin (19).

There remains some disagreement whether digestion of absorbed protein in the lysosomes represents the final step in protein reabsorption. The question is whether absorbed LM are entirely digested in the proximal tubule cells or whether at least portion may escape and be returned to the circulation. As listed by Maack (15), three lines of evidence indicate that considerable intrarenal digestion must occur: *1*) absorbed proteins can be localized within secondary lysosomes which contain cathepsins; *2*) these lysosomal fractions can readily hydrolyze absorbed proteins; and *3*) bilateral nephrectomy increases plasma concentration and/or plasma half-life of LM. On the other hand, a significant fraction of absorbed lysozyme is present in the cytosol (17). The direct relationship observed between the amount of lysozyme injected into mice and ratio of the protein in lysosomes to that in cytosol suggested that lysosomal involvement in tubular handling of lysozyme represents a response to protein overload. Additional results support the possibility of transcellular movement of lysozyme. The evidence includes the observation (16) that lysozyme injected into flounders is subsequently partly released from tubules in vitro. Because under these conditions tubules essentially form closed sacs, the protein is presumably released across the basement membrane. Similar evidence was obtained with intact rat kidneys perfused in vitro after in vivo injection of lysozyme (15); the observed appearance of lysozyme in the perfusate could only have resulted from its extrusion from tubular cells. In contrast, Christensen and Maunsbach (6) could recover only 4% of total activity as labeled protein when rat kidney cortex slices were suspended in a leaching medium following the in vivo injection of labeled lysozyme.

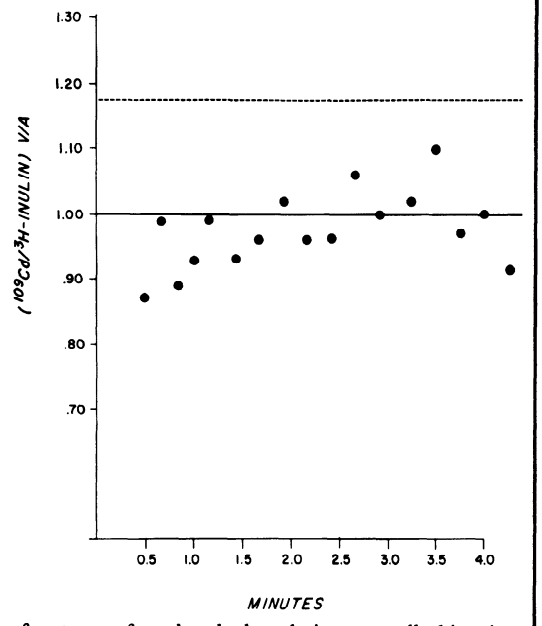
There is little indication that other proteins return to the circulation intact after their tubular absorption. For instance, in patients with renal disease, plasma levels of myoglobin and β_2-microglobulin are significantly and inversely correlated with glomerular filtration rate as measured by clearance of ^{51}Cr-ethylenediaminetetraacetic acid and directly with plasma creatinine concentration (12); the close correlation between changes in

Figure 4



Influence of myoglobin and lysozyme on binding of cadmium metallothionein (cdMT) to brush border membrane (BBM) (modified from Ref. 30). Membranes bind CdMT at two classes of sites: high-affinity sites (*A*), saturated at low CdMT concentration, and low-affinity sites (*B*). At high CdMT concentration (20 μg/ml) binding occurs at *A* + *B;* at 1 μg/ml primarily *A* is involved. Effect of myoglobin is shown at *A* (□) and *A* + *B* (○) that of lysozyme at *A* (▲).

Figure 5



Absence of return of reabsorbed cadmium metallothionein (CdMT) to circulation (Foulkes, unpublished data). For details, see text.

creatinine and β_2-microglobulin concentrations in plasma suggests that neither compound is reabsorbed. A direct test of the possible return of reabsorbed CdMT into renal venous blood is shown in Fig. 5. Here the ratio of Cd to inulin was measured in renal arterial and venous plasma during arterial infusion of ^{109}CdMT and [^{3}H] inulin. Fractional reabsorption of CdMT was calculated from the isotope ratio in urine collected during the infusion, and the filtration fraction was derived from the inulin extraction. Reappearance of all absorbed protein in venous plasma should have led to a venous Cd enrichment and thus increased the isotope ratio in venous compared with arterial plasma as shown by the dotted line. Absence of such venous Cd enrichment indicates that during the period of observation none of the reabsorbed protein was extruded from cells.

In summary, the tubular reabsorption of LM involves a rate and specificity determining interaction with the brush border membrane, followed by endocytotic uptake into cells and probable intracellular digestion. The observation that hemoglobin resembles myoglobin in inhibiting CdMT absorption (10) suggests that high molecular weight proteins react with the same membrane sites as do LM; the involvement of both endocytosis and lysosomal accumulation/digestion in tubular absorption of high and low molecular proteins has already been referred to. It is likely therefore that LM absorption proceeds by mechanisms at least qualitatively similar to those responsible for reabsorption of high molecular weight proteins.

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Book Reviews

The Endometrium; Hormonal Impacts. J. de Brux and J.P. Gautray (Editors)

New York: Plenum, 1981. 162 pp., illus., index, $29.50.

This brief publication represents the assorted papers given at a symposium on "The Physiology and Pathophysiology of the Menstrual Cycle" held in April 1980. As such, the volume includes nine varied but related communications ranging from a discussion of steriod receptors in the endometrium to an ultramicroscopic study of the "Luminal uterine epithelium during the human menstrual cycle." These communications bring together a wide body of data quite readily available from numerous other sources. This reviewer sees little merit in still another communication of this information unless accompanied by at least some attempt at reinterpretation or analysis. Since the symposium's discussions are not included, this aspect is sorely lacking.

The volume does, however, convey the extraordinary advances made in our comprehension of the hormonal and morphological changes that characterize the endometrium during the menstrual cycle, during implantation, and in the development of endometrial hyperplasia and carcinoma. Each of these topics is briefly and succinctly reviewed by authoritative contributors. However, the treatment of these complex phenomena is not sufficiently comprehensive or novel to justify another publication.

Thus, if one attempts to derive the special message the contributors are trying to convey regarding *The Endometrium,* no special information or guidance comes to this informed reader, and the chapters also fail to provide the uninitiated with a proper orientation to the subjects in hand.

Roy Hertz
George Washington University

Estrogens and Brain Function: Neural Analysis of a Hormone-Controlled Mammalian Reproductive Behavior. D. W. Pfaff.

New York: Springer, 1980. 273 pp., illus., index, $24.50.

This monographic exposition is a very precise and explicit account of the penetrating studies done by the author and his colleagues on the hormonal and neurological aspects of mammalian lordosis. As such, it provides a valuable presentation of these extensive observations on a clearly defined problem of neuroendocrine control of a specific pattern of reproductive behavior, mainly in the female rat.

Accordingly one may find the first portion of the title misleading and the second segment of the title inaccurate, since only the "neural" aspect is indicated. Actually Dr. Pfaff's significant contributions relate to a hormonally regulated behavioral response mediated though the complex neural pathways he has so lucidly dissected.

There is presented a stepwise experimental analysis of the lordosis response as effected through specific peripheral sensory pathways, spinal interneurons, ascending neural pathways, brain-steroid interaction with emphasis on the hypothalamus, and the highly complex effector mechanisms involved.

For a reader who wishes to be informed regarding our current knowledge of a specific neurohumoral effect and the resultant motor behavioral patterns, this book will provide a handy and authoritative review.

In addition, in two closing chapters entitled "Summary" and "Epilogue" the author all-too-briefly puts the assembled data into a sort of perspective in relation to general problems of behavior and their analysis. One would have hoped that more emphasis be given to this area so that what is otherwise simply an essentially expanded laboratory notebook may have proved to be provocative.

Roy Hertz
George Washington University

Disturbances in Neurogenic Control of The Circulation. F.M. Abboud, H.A. Fozzard, J.P. Gilmore, and D.J. Reis (Editors)

Bethesda, MD: Am. Physiol. Soc., 1981. 274 pp., illus., index, $38.50

This book is another volume in the Clinical Physiology Series published by the American Physiological Society and presents some of the most recent findings and hypotheses on the integrative aspects of neural control of the cardiovascular system. The eighteen chapters deal with several of the possible neural mechanisms that may be involved in various pathophysiological states of cardiovascular regulation.

The text is divided into three major areas of abnormal neurogenic control of the circulation. The first five chapters discuss abnormalities in neural control related to cardiac hypertrophy and failure. Emphasis is placed on the function of cardiac sensory receptors during normal adjustments in the circulation and those that take place during congestive heart failure and hypertension.

The second section contains seven chapters dealing with central nervous regulation of arterial blood pressure and hypertension. The role of various levels of the CNS, including both brain stem and forebrain, neuropeptides, arterial baroreceptors, and volume receptors in blood pressure regulation are discussed.

The final section, containing six chapters, is devoted to neural control of the heart during arrhythmic activity. The chapters discuss at a cellular membrane and biochemical level the various processes that mediate the effects of the autonomic nervous system on cardiac tissue. The role of autonomic regulation of sinus node activity and of atrioventricular conduction in initiation of arrhythmias is reviewed and discussed.

In contrast to some similar books, this one contains uniformly well-written papers and is superbly edited and organized. Most of the articles discuss recent data and avoid extensive reviews of past literature, which can be found elsewhere. However, each report contains a list of pertinent and recent references that provide the reader with an excellent source for a more complete literature search. This book presents an up-to-date comprehensive discussion of several important aspects in autonomic neural regulation of the circulatory system. Although a valuable addition to any medical library, I recommend this book to those interested in keeping abreast of the expanding area of abnormal neural regulation involved in hypertension, heart failure, and arrhythmias. The strong emphasis on pathophysiology and the inclusion of chapters discussing human studies make this text an important one, not only for the basic investigator but also for the clinician as well.

D.O. Nelson
Northwestern University Medical School

Physiology and Technology of Reproduction in Female Domestic Animals. R.H.F. Hunter

New York & London: Academic, 1981. 393 pp., $60

This excellent book contains 12 chapters dealing with the intricacies of the reproductive process of the female domestic animal, excluding the chicken, dog, cat, and goat. The organization is more or less consistent in that the basic physiology underlying the various aspects of reproduction is presented and discussed in reasonable detail that will satisfy the undergraduate student but is not sufficiently detailed for the needs of the more advanced graduate student. After the basic groundwork has been laid, ways to modify the normal functions of the reproductive process are discussed and documented with data. Among other topics, means of modifying the estrous cycle, control of ovulation, artificial insemination, implantation and establishment of pregnancy, in vitro fertilization and embryo culture, transplantation of embryos, diagnosis of pregnancy, control of parturition, and restoration of fertility are discussed. The final chapter deals with future developments that can be foreseen in the modification of the reproductive process for purposes of greater efficiency.

If one must find fault with the book, it is that the data selected for presentation are usually the most optimistic illustration of any given manipulation or modification of a process. It is not always made clear that experiments not cited frequently have a much lower success rate than those cited in the book. This tendency is of course understandable in that the book is intended to illustrate a basic process and not necessarily to present a complete evaluation of the available data. Each chapter is followed by a list of references that are satisfactory for the beginner. The more advanced student could probably be better served by references to more sophisticated review articles rather than citations of research papers.

The book is clearly written and no major errors were noted. The main drawback of the book is its price ($60.00), which is probably dictated by the profuse use of full-page color illustrations. A number of them are of questionable value: for instance, Fig. VIII.3, which is supposed to illustrate embryo transfer. On the other hand, such figures as VI.8 showing the mode of attachment of fetal membranes are quite good and show what is intended. I would recommend that for future editions the color illustrations be examined carefully and that some of them be replaced by good black-and-white photographs. All in all, this is a good book which belongs on the shelf of students and their teachers.

A.V. Nalbandov
Biology of Reproduction

The Prostaglandin System: Endoperoxides, Prostacyclin, and Thromboxanes. F. Berti and G.P. Velo (Editors)

New York: Plenum, 1981. 428 pp., illus., index, $49.50

The Prostaglandin System rates as one of the best current volumes in providing an overview of prostaglandin biosynthesis, metabolism, and the most important functional roles of prostaglandins in physiology. At the outset, five chapters discuss biosynthesis and metabolism with a newer slant to include the importance of phospholipids and phospholipase activation in regulating arachidonate metabolism. The concise, refreshingly presented summaries of the biosynthesis and metabolism of prostaglandins and thromboxames are nuggets of pertinent information of particular interest to the laboratory investigator and not often characteristic of reviews of this kind. Chapters review techniques for the assay and bioassay or arachidonate metabolites and provide warranted criticisms and cautions in their use. Several chapters are devoted to describing the most recent theories on the mode(s) of action of steroidal and nonsteroidal anti-inflammatory agents. Chapters on prostaglandin analogue antagonists and the use of pharmacologic agents in modulating arachidonate metabolism are included. Major sections of the text are reserved for authoritative discussions of the role of prostaglandins in inflammation and the participation of free radicals and lipid peroxidation in arachidonate metabolism; prostacyclin and its involvement in vascular reactions and atherosclerosis; the importance of prostaglandins in blood pressure regulation and renal function; the gonadal and reproductive functions of prostaglandins; arachidonate metabolites and airway function, histamine, and slow-reacting substances; and arachidonate metabolites, their receptors, and roles in the GI system. Prostaglandin involvement in carcinoma development is also discussed. Instructive models or diagrams have been included. The only major fault of the volume lies with the inappropiate placement of a few chapters, which disrupts the development of major sections. The text is readable, and sections have been contributed by familiar authors as well as newer arrivals on the review circuit. This contribution to the advanced study series makes a worthwhile broad-scope reference for students of prostaglandin research.

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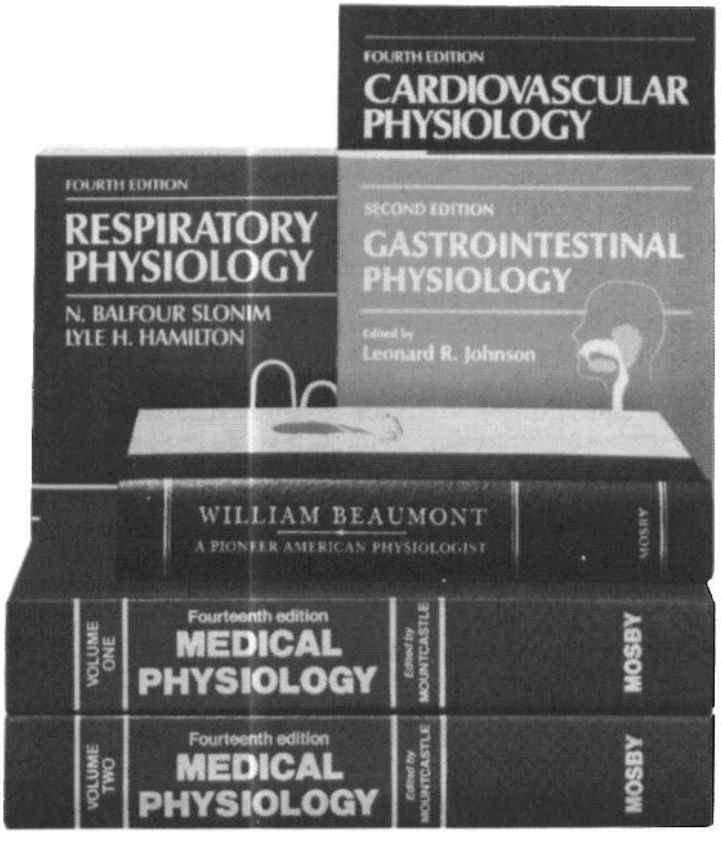

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