THE PHYSIOLOGIST

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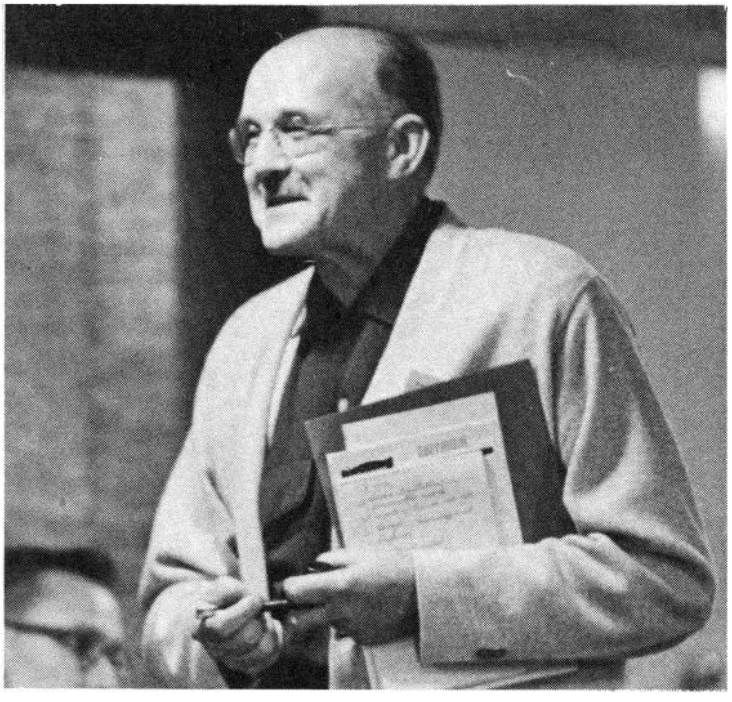
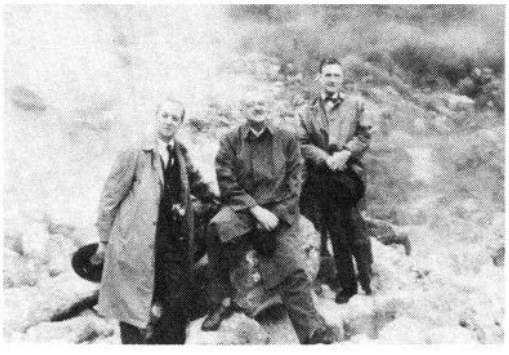
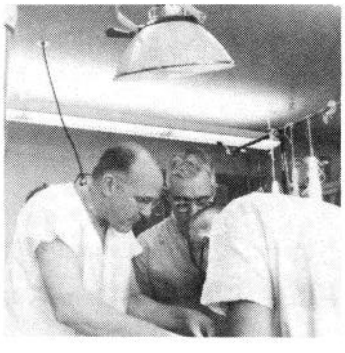
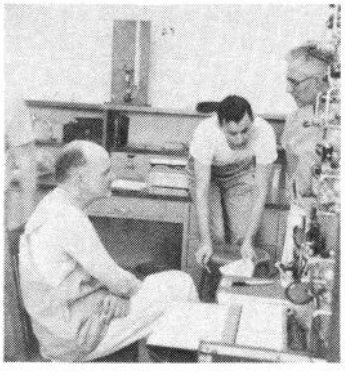
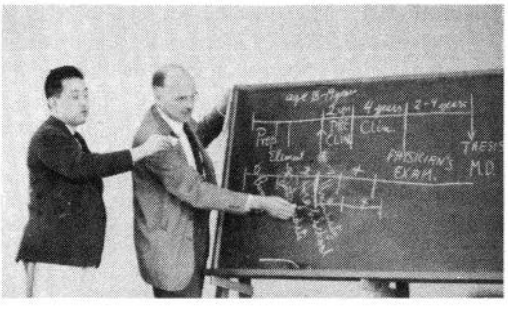
Cover: Maurice B. Visscher











Maurice B. Visscher and colleagues.

Maurice B. Visscher (1901–1983) Scientist and Humanitarian

Maurice Visscher's tremendous impact on so many facets of both our scientific and nonscientific life should be credited to his major contributions to scientific knowledge. These gave him both the platform and the credibility that he needed in his efforts to create an environment conducive to productive research for his fellow scientists as well as to improve the lot of his fellow man the world over. There undoubtedly were others in the scientific community who shared his views on fostering international scientific and governmental cooperation in all matters, especially in nuclear disarmament, on the increasingly momentous problems in scientific communication, on the scientist's civic obligations including the necessity to combat governmental encroachment on our civil liberties, and finally, who shared his empathy for the hungry and suffering in his own country and the world at large. What is clear, however, is that Maurice Visscher was able to discern the most significant of the myriad of problems facing science and humanity in the middle and final third of the twentieth century, and fortunately for us, the international stature he had derived from his scientific contributions permitted his voice to be heard at the highest levels of both scientific governing boards and the halls of government. It would be easy for anyone with such scientific and political influence to be seduced into uncritical sycophancy or blind acquiescence to scientific or governmental policies, whether or not they were just, in order to maintain his proximity to the seats of power, but that was not in Maurice Visscher's character. At critical moments in his life he did not hesitate to break with long-time friends—Vice President Hubert Humphrey in the political arena over the Vietnam conflict and Owen Wangensteen in the area of university governance—rather than acquiesce in decisions he considered detrimental to the country in the one case and the University in the other. Where his adversaries of the moment were well intentioned, as in these two instances, his forgiving nature permitted a later reconciliation with the continuation of warm and highly productive friendships. Even in what may be considered to have been the most important decision of his life, he remained true to principle and elected to be treated for his critical illness which proved terminal just as any other member of the HMO he helped to found, the first HMO in Minnesota and one of the first in the country. The foregoing is not intended to cloak him in a mantle of righteous infallability, for he did make mistakes, but most frequently these grew out of a kindly desire to help someone in difficulty. The thought I would most like to leave with the reader is that to every endeavor that he undertook throughout his life, and these were legion, he made major and unique contributions because of his incisive intellect, the extremely wide range of his knowledge, and his abiding humanity. He was a true Renaissance man—scientist, humanitarian, philosopher, educator, and political reformer—who had published seminal contributions and consequently was preeminent in all of these fields (2, 3, 6). His passing can only be viewed as leaving a major void, one not likely to be filled soon.

Turning first to his scientific contributions, as appears frequently to be the case with someone destined to become an outstanding scientist, Maurice early on showed an aptitude for experimental science, having performed, as a senior at Hope college, an elective study on bacterial and organic pollutants in the stream into which the town where the college was located dumped its raw sewage (5). Considering the time at which this study was performed, the prescience of this young scientist will not be lost on the reader. During study for the combined M.D.-Ph.D. degrees in the scholarly yet administratively permissive environment created at the University of Minnesota Medical School by Dean Elias Potter Lyon, his mentor Frederick Scott encouraged him to minor in physical chemistry, which Maurice felt uniquely prepared him to attack basic physiological problems, such as that of material transport, in which he felt he had made his greatest contribution. A series of cleverly designed experiments by Visscher and his students made possible the unequivocal conclusion that certain ions were actively transported across the intestinal mucosa. While he was helped by his early access to isotopes at the University of Minnesota, it should be noted that his extremely clever studies without the use of isotopic tracers had already led to this conclusion. His studies also established the bidirectional movement of water across the intestinal mucosa. As the noted gastrointestinal physiologist, Charles Code, who had been a postdoctoral student in Visscher's laboratory and who remained a lifelong friend so aptly put it, "There is no area in his multi-faceted career in which Visscher's virtuosity was more brilliantly displayed than in his studies of intestinal transport. He was really plowing new ground—all alone." (1).

Although there was a steady flow of papers on intestinal absorption from his laboratory, most of Visscher's work was in the area of cardiovascular physiology. This is not surprising, since his career in physiology was launched with a National Research Council (NRC) Fellowship with Ernest Starling, a sojourn so successful that, in addition to resulting in an important paper with Starling, "The regulation of the energy output of the heart," an area he was to pursue for some years, also "inextricably linked" his name with the "Starling Law of the Heart" (1). Furthermore, as pointed out by Earl Wood at a symposium on the occasion of Dr. Visscher's 75th birthday, the experiments on heart-lung preparations of Gordon Moe and Visscher, performed 45 years ago, already indicated the existence of a family of Starling curves, each one reflecting the prevailing neural (autonomic) and physical-chemical conditions and their effect on the mechanical efficiency (contractility) of the heart. Also, Moe and Visscher showed that diastolic fiber length determined the O_2 consumption, i.e., the energy liberated by the

heart, and that as the heart progressively failed, less and less of this energy was converted to useful work, a decrease in mechanical efficiency reversible by therapeutic doses of the cardiac glycosides. These results presage concepts that are still widely held today. Following his stint with Starling, in a second NRC postdoctoral fellowship in A. J. Carlson's laboratory at the University of Chicago, he had the good fortune to come in contact with. Baird Hastings, from whom he learned the views and methodology of the Van Slyke school, which eventuated in his discovery of the pH dependence of the actions of the catecholamines on the microvasculature.

While his contemporaries and his students do not need to be reminded of the widely different areas of physiology to which Maurice Visscher made significant fundamental contributions, for other readers it may be appropriate to mention that, in addition to the primary areas of cardiovascular and gastrointestinal physiology already mentioned, his studies also encompassed the areas of nutrition, pulmonary function, cancer biology, chronobiology, renal physiology (tubular transport), oximetry, pulmonary edema, endotoxin shock, and aging. Nor were these the isolated forays of a dilettante, for each of these areas received an amount of attention sufficient to generate at least several publications and, in most cases, an even greater number, spread out over a number of years, evidence of a continuing deep interest in these different areas.

In addition to his scientific output, another "coin of the realm" of the scientist is the students and coworkers whose careers he has influenced through contact with them in his laboratory. Here again Maurice Visscher excelled, having had as students or collaborators such basic scientists as G. K. Moe, E. H. Wood, H. E. Essex, J. F. Herrick, R. B. Dean, J. J. Bittner, C. F. Code, C. Martinez, F. J. Haddy, E. B. Brown, A. O. Nier, P. F. Salisbury, H. R. Warner, and O. Jardetzky and such clinical scientists as H. B. Burchell, C. Dennis, R. L. Varco, F. J. Kottke, G. S. Campbell, C. W. Lillihei, E. B. Flink, L. D. MacLean, W. W. Spink, and J. B. Aust. All of these basic and clinical scientists, most of whom were his students, reached professorial rank and most attained national and international stature, which is probably a better measure of Visscher's influence on biomedical science than the number of his scientific publications, which, however, was enormous, considering the care with which each one was prepared. Thus it is clear that he had earned his scientific credentials the hard way and left us a legacy of outstanding students and collaborators to disseminate and perpetuate his approach to scientific problems as well as his ideals.

But his prodigious and highly innovative scientific output hardly gives the true measure of the man. His scientific contributions and the numerous honors stemming therefrom merely served as a vehicle permitting him to exercise his deeply felt civic and humanitarian obligations. It is difficult, at this point, to determine whether the scientific or the civic and humanitarian activities took precedence in his mind, a fact which alone tells us much about the man. What is clear, however, is the fact that he willingly pursued a wide variety of humanitarian and civic activities at the expense of his scientific productivity, and there is no telling what great scientific insights he sacrificed selflessly in order to be of help to his fellow man. While it is certain to sound like the well-worn cliche which it is, the reader will have to accept as fact that it is simply impossible to even list the myriad of science policy, civic, and humanitarian activities in which he participated, so that a highly abbreviated, selected sample, in addition to those already mentioned, will have to suffice.

Years ago, as a department chairman at an early age, successively at the Universities of Tennessee, Southern California, Illinois, and Minnesota, he astutely foresaw the magnitude of the threat to experimental medicine and biology posed by the antivivisectionists and consequently devoted a great deal of effort over his entire lifetime to this important cause, the true significance of which scientists in certain parts of our country have only recently come to appreciate, as they lost access to inexpensive experimental animals in favor of the senseless destruction of these animals in the pounds.

As a humanitarian, he served as scientific head of a post-World War II UN and Unitarian relief mission to Italy. Moreover, he used the significant political influence he had gained successively at the local, state, and national levels by his selfless time-consuming support of compassionate liberal political candidates in his lifelong struggle to gain acceptance of the concept that providing a decent standard of living and equal opportunities for all of its citizens is a legitimate obligation of government. As chairman of the special Committee on Civil Liberties of the AAAS, which he caused to be set up, he fought the tyrannical witch-hunting harassment of scientists of the Joe McCarthy-House Unamerican Activities Committee era at the cost of having his own loyalty to his country called into question by what have now clearly become known to have been demagogic power-hungry legislators. As in many other areas, time has vindicated Visscher's opinions in this matter of the governmental questioning of the loyalty of our country's scientists also; for with each passing day we are treated, via the freedom of information act, to more evidence of governmental frame-ups, while the evidence of American scientists having committed disloyal acts against their country turns out to be more and more discredited. The cost of this dark episode in our history in damaged careers and lives and in curtailed productivity in science and in the arts, already recognized by Visscher long ago, is just being appreciated by the public at large.

Visscher, as a member of the Minnesota Governor's Committee on Atomic Energy, was among the first in this country to warn against the danger of radioactive contamination of our food chain from above-ground nuclear explosive testing and caused regular testing of milk and grain products for such contamination to be instituted.

He also made major contributions to the identification of the problems and to the outlining of their solution in the important area of scientific communication, both at the scientist-to-scientist and scientist-to-general public levels, problems stemming largely from the unprecedented support for biomedical research in the last quarter of a century. In a relatively recent article (7) he decried the current chaotic "nonsystem" of scientific publication for its editorial censorship and for publisher's attempts to restrict journal article reproduction rights, neither of which is in the interest of the scientist-author nor of the public at large, which ultimately paid

for the research being communicated. He had the courage to question the wisdom of the current censorship system that is intended to protect the "authors against themselves" rather than permitting readers to make their own evaluations and ignores "the personal biases or even the selfish interests of referees," which may be the basis for the rejection of manuscripts. His interim remedy was the substitution of informative abstracts with a national repository making available copies of the complete manuscripts, with an international computerized storage and retrieval system as the ultimate solution. In the area of the scientists' communication with the general public, he feared that allocations of large sums of money for specific practical results would unrealistically heighten the public's expectation of instant cures, whereas successful practical solutions to medical problems are based on years of preceding, painstaking, basic research (4), with the failure to achieve immediate results likely leading to the public's disillusionment and a consequent loss of support for science. Finally, he played an important role in permitting *Biological Abstracts* to continue functioning and in developing the program of *Annual Reviews,* and he personally conceived and was chairman of the committee that oversaw the production of the *Handbook of Physiology* series, which has proved to be a valued reference source the world over.

Turning now to Maurice Visscher, the man, he was a quiet thoughtful man of great compassion. He would take the time to help anyone who needed it and no request for help was ever turned down, be it assistance for an indigent student or funds for a physician's journey to aid the suffering in Chad. In discussing scientific matters, despite his vast knowledge, he was not at all intimidating, so that no one felt constrained to hold back ideas or judgements, with the end result that no new thought or idea was ever lost on his account. His brilliant insights, coupled with his selfless devotion, made the beleaguered participants of what appeared initially to be hopeless causes, such as the anti-Vietnam War effort, feel that their labors were not wasted. And he was often successful, in spite of the odds. The same courage that permitted him to stand apart from the crowd and go against current dogma in scientific matters pervaded all of his actions. When he thought something was the right thing to do, he was unshakable, and the greater the size of the opposition, its social rank, or political power, the more tenacious and steadfast he became in his beliefs. He was for the underdog, and no just cause was too small, no minority group too underprivileged or powerless, no individual too weak or inconsequential to merit his sincere whole-hearted support. And this support was not trivial. For example, where a senior Congressman's office and the Vice President's office were ineffectual, he succeeded in fashioning a strategy that prevented the Immigration Service from forcing a brilliant young graduate student to return to his native country, which was governed by an oppressive dictatorship and in which he might likely have come to harm. His friendship was warm and genuine, and he could always be counted on for encouragement and support in times of stress. Rather than list the numerous honors he was awarded, it is considered preferable to have detailed some of the reasons he deserved them. At the end he said he had no regrets—he had had a full life and the companionship of a wonderful family and had been fortunate in many other respects. Since one cannot imagine him refusing assistance to anyone in our society, in fact to anyone at all, or permitting injustice anywhere on the globe to go unchallenged, all the world's people have lost a friend. We will not see his like again soon.

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Irwin J. Fox

Departmental History

Department of Physiology Boston University School of Medicine (1873–1948)

The Trustees of Boston University opened their first, or Homeopathic, School of Medicine on Wednesday, November 5, 1873. The school was opened to students of both sexes, on uniform terms and conditions. "Separate cloak and retiring rooms are provided in the college building for the use of lady students." Note the designation of "lady students," which had always been used in preference to "female students" during operation of the previous school, the New England Female Medical College (8).

The first dean was Israel Tisdale Talbot M.D., who continued as dean for 23 years until 1896 and then served as director of the Homeopathic Hospital from 1897 until his death in 1899. According to the Historical Register of Boston University (BU), 1869–1901, and annual catalogues of the Boston University School of Medicine (BUSM), Dr. John P. Sutherland served as acting dean from 1896–1899 and then as dean from 1899 to 1923. He continued as dean emeritus and Professor of Medicine from 1923 until his death in February 1942. Soon after reorganization of faculty and curriculum in BUSM during the period 1918–21, Dr. Alexander S. Begg was appointed dean in 1923 and served in this capacity, as well as Waterhouse Professor of Anatomy, for 17 years until 1940. Dr. J. Leroy Conel, Waterhouse Professor of Anatomy, was chairman of an administrative committee acting in lieu of a dean in 1940; Dr. Bennet F. Avery, Waterhouse Professor of Anatomy, was dean from 1941 to 1943, followed by Dr. Charles F. Branch, Professor of Pathology, 1943–45, Dr. Donald G. Anderson, Assistant Professor of Medicine, 1945–47, and Dr. James M. Faulkner, Professor of Clinical Medicine, 1947–55. This rapid turnover of deans has prevailed during the last two decades, five deans and two acting deans having officiated during 1955–71. Thus 11 persons have served as deans or acting deans of BUSM between 1940 and 1971, an average term of office of 2.8 years.

A complete account of the first 75 years of physiology at the Boston University School of Medicine by E. R. Loew (professor emeritus and former chairman of Dept. of Physiology BUSM) and a foreword by E. W. Pelikan (professor and chairman of Dept. of Pharmacology and Experimental Therapeutics BUSM) have been deposited in the APS archives.

Only two buildings were occupied by BUSM at the beginning of its operations in 1874. The first was the present central portion of the Massachusetts Homeopathic Hospital built by the New England Female Medical College; this is presently known as the Talbot Building. The second building, the BUSM (first called the College Building and later designated as Building C), was constructed in 1873. This building (100 × 35 ft; 4 stories) contained a large amphitheatre, a lecture room, offices for deans and professors of anatomy and chemistry, and laboratories for anatomy and chemistry, which were equipped and arranged to accommodate about 50–60 students (7; 1891 cat.). There is no indication whatsoever that the Department of Physiology was allocated office space or laboratory facilities in Building C. It is unlikely that any extensive laboratory exercises in physiology were included in the curriculum until BUSM erected Building B soon after 1890, although the 1889 catalogue mentions "experiments and instruction in the physiological laboratory" offered by Professor John Rockwell.

The annual catalogue of BUSM for 1891 pictures the detailed floor plans for Building B, a structure four stories in height and connected with Building C. This building was probably completed between 1891 and 1893. The first laboratory in Building B used by the Physiology Department consisted of three rooms on the first floor of the building, later occupied by Biochemistry when the physiology laboratories were moved to the fourth floor.

Several features of the physiology laboratory should be noted. It was located on the first floor, the library was on the third floor. The physiology laboratory provided work space for students with a wall counter on two sides of the room (28 × 50 ft) and only a few movable tables. Thus separate tables were probably not provided to pairs or groups of four students. It was stated (7; 1894 Cat.) ". . . There are at present a number of the most approved pieces of apparatus for studies in physiology and hygiene, and to these frequent additions will be made . . . and experimental physiology is required of all the students of the second year" (80–100 hours).

Clinical Teaching and Training in BUSM—Early Years

During the first few decades of BUSM's history, much of the clinical teaching and training took place in Boston City Hospital, the Homeopathic Medical Dispensary (later known as Central Dispensary), and the Massachusetts Homeopathic Hospital.

The first "circular" or *School Bulletin* (1873) lists as Prof. of Physiology, Joseph R. Buchanan M.D., Syracuse, NY and as lecturer in physiology, Archibald K. Carruthers M.D. The bulletin for the following year (1874) lists Archibald K. Carruthers M.D. as professor of physiology. Walter Wesselhoeft M.D. became a professor of three different subjects in 4 years (1873–75, prof. of anatomy; 1875–76, prof. of physiology; 1877, prof. of obstetrics and physiology). Later appointments were Howard P. Bellows M.D., lecturer on physiology,

1877-79 and professor of physiology, 1880-83 (he then served for many years as prof. of otology through 1929); Herbert A. Chase M.D. lecturer on physiology, 1884; John A. Rockwell M.D. lecturer on physiology, 1885-87; and Albert H. Tompkins M.D. assistant in physiology, 1886 (he served as professor through 1898; and also taught Sanitary Science).

Dr. John A. Rockwell, Professor and Head of Physiology

The reader should consult the "Reminiscences" by Dr. Watters (1) for his informative comments concerning the Department of Physiology and the activities of Professor Rockwell, who was chairman of the department from 1888 to 1899 except for two years, 1890-92.

Information obtained from annual BUSM catalogues (1888-1891) and from the student publication *The Medical Student* and other sources (11, 12) indicate that Professor Rockwell was very successful in organizing and presenting course offerings in physiology and initiating laboratory exercises first mentioned in 1889 (before completion of Building B, probably in 1891). The following excerpts from *The Medical Student* from 1888 to 1897 are most informative.

1888, Oct., vol. 1(1)—Drs. Sutherland and Rockwell have been promoted to professorships, and can be depended upon to ably fill their respective positions. The ups and downs of the chair of physiology have been many and varied, and we feel a sense of rest and satisfaction to know that it is now placed in efficient, and we earnestly hope permanent hands; the only remaining wish is to see the course itself amplified and extended, to cover the full first year.

1889, April, vol. 1(7)—Professor John A. Rockwell has returned from Europe, where he has made a special study of physiology. He will lecture at 10 a.m. every day, during the remainder of the term.

1890, Oct., vol. 3(1)—No student can fail to appreciate Professor Rockwell's gift of the new electric clocks, which, at no small expense, were put into the college during the summer vacation.

1891, Nov., vol. 3(2)—Dr. Rockwell's new laboratory is a marvel of neatness and convenience. The school stands sadly in need of increased space. Microscopical and physiological laboratories are essential, and for the best work need the best of conveniences. A large laboratory for obstetrics would not be remiss.

1891, Dec. vol. 3(3)—The Juniors have taken their final examination in Physiology, after the best course of instruction in this branch yet given in the college . . .1891 Prof. Rockwell sailed for Europe as soon as his course of lectures was finished [i.e., in April or May of 1891; the second trip in two years].

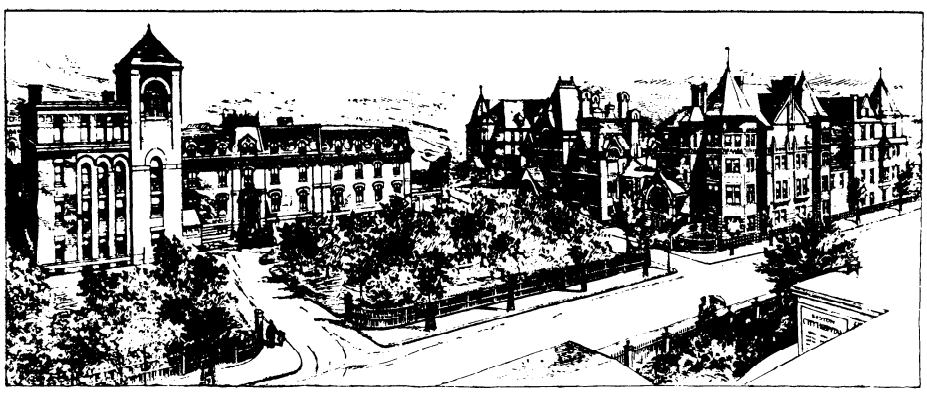
1892, Oct., vol. 4(1): 408—Dr. John A. Rockwell has resigned, and Dr. Geo. E. May has been appointed Lecturer of Physiology.

1897, May, vol. 9(7): 109—Professor Rockwell's students are working hard at their final tasks. In no school in this country, not excepting Johns Hopkins, is the laboratory course in Physiology so broadly planned.

Recommended Textbooks for Physiology

For about a decade (1888-97) the BUSM faculty listed in the annual catalogue the textbooks recommended for study and reference. The early physiology texts were by Foster, Dalton, Flint, and Martin and in 1897 a textbook by Howell was recommended for second-year students. The first books concerning laboratory experiments and instruction were recommended in 1890, one year after laboratory instruction was first offered to students. These books were McGregor Robertson's *Physiological Physics* and Starling's *Practical Physiology*.

From Professor Rockwell's own writings it is apparent that he insisted that medical students should spend appreciable time in the experimental laboratory. In discussing methods of instruction in physiology by use of textbook, lectures, and experimental work (11), he emphasized the latter and described the content of the laboratory course offered in BUSM in 1893. More details appeared in Rockwell's article entitled "A course in experimental physiology" (12). Beginning in 1890, all medical students were required to pursue a 4-year course of instruction. The first 4-year course of graded medical instruction ever offered in this country was instituted in BUSM in the spring of 1878, but for 12 years the students could choose this course or the older 3-year course. However, in the summer of 1890, the faculty decided to make the longer one the required course for all students. Although the announcement was made that the change would go into effect in the fall of 1891, when several students anxious to begin the new course without delay, immediately appeared, provision was made for them, and the required 4-year course began in the fall of 1890. Since that date the requirement has been 4 years of professional study before promotion to the degree of doctor of medicine.



The campus, as it appeared in about 1900. Building B, with its tower, is at the extreme left. The College Building (Building C), with its mansard roof, is to the left of center. [From BUSM 34th Annual Announcement and Catalogue, June, 1906].

Tenure of Physiology Chairmen, BUSM (1888–1948)

The tenures of chairmen of the Department of Physiology are as follows: Dr. John A. Rockwell, Sr., 1888–90; no professor or chairman listed with faculty (Prof. Rockwell in Europe), 1890–92; Dr. John A. Rockwell, Sr., 1892–98; no professor or chairman listed with faculty, 1899–1901; Dr. F. P. Batchelder, 1902–21; Dr. Frederick H. Pratt, 1921–42; Dr. Leland C. Wyman, acting chairman, 1942–45; Dr. Hans O. Haterius, 1945–48; and Dr. Earl R. Loew, 1948–69.

It is informative to consider the objectives and content of the teaching programs in physiology (and other disciplines) at this period in the history of BUSM. Excerpts (below) from the 33rd Annual Catalogue of 1905 describe methods of instruction, relative emphasis on didactic vs. laboratory and clinical work, emphasis on techniques, description of laboratories and equipment, and so forth.

Methods of Instruction

> The methods of instruction are those which have proved themselves most successful in past experience. Didactic lectures have been largely supplanted by laboratory and clinical work. During the first two years the work of the student is largely in laboratories where, in addition to laying a broad foundation for future studies, particular attention is paid to training in technique, to developing the power accurately to observe and the ability correctly to record observations and the results of experiments, and to stimulating the desire to make original investigations. During the third and fourth years, in addition to lectures, recitations and laboratory work, the instruction includes individual and class work in the extensive hospital and dispensary clinics at the disposal of the Faculty. In these clinics students not only have the opportunity to see a great variety of diseases, but each student receives instruction in the best methods of examining patients. This instruction includes practical training in physical diagnosis by palpation, percussion, the use of ophthalmoscope, laryngoscope, stethoscope, phonendoscope and all the modern diagnostic aids. The "conference system" and the "case method" have passed successfully through the experimental stage and have demonstrated their marked usefulness as methods of instruction.

In comparison with many medical schools, BUSM was offering laboratory work in basic sciences which was highly commendable as evidenced by specific statements in the Flexner Report on Medical Education (6). Laboratory work certainly did not largely supplant lectures, since in 1905 there were 140 lectures and 180 hours of laboratory work in physiology and 128 each of both lecture and laboratory work in chemistry during the first two years. However, the faculty had reason to be proud of their ability to offer a commendable amount of laboratory work in spacious well-equipped laboratories.

Laboratory Facilities

The emphasis placed on facilities for student experimentation, laboratory experiments, and study of museum specimens is indicated by photos presented in the annual catalogues, especially for the years from ca. 1894 to 1908. Several photos reveal that at least some groups of students were provided with kymographs for recording on smoked paper. It is very likely that this equipment had to be imported from Germany; if so, kymographs probably cost $200 each. Physiologists were not able to purchase American-made equipment at lower cost until after 1898, when Dr. Wm. T. Porter formed the nonprofit Harvard Apparatus Company, which constructed and sold kymographs, inductoria, tambors, muscle levels, and so forth. It is also apparent that the laboratories contained substantial equipment before Dr. Arthur Weysse was first engaged as instructor in experimental physiology in 1899. As early as 1891–93, BUSM had acquired some equipment for the physiology laboratory, but more was needed at an estimated cost of $5,000, as indicated by pleas made to alumni (11, p. 11; 12, p. 31) and to faculty and public benefactors (13).

Laboratory Course

> Experimental physiology. Laboratory work by each second year student during one half year [consists of] one hundred and eighty or more hours. The aim is to elucidate selected subjects and to train in technique and laboratory methods. The phenomena of the nerve-muscle preparation are studied in detail by a carefully selected and extended series of experiments, supplemented by occasional lectures with written and oral quizzes, special emphasis being laid on correct interpretation of observed results. This work is succeeded by a study of the circulation; the artificial circulation scheme, stethoscope, phonendoscope, cardiograph, sphygmograph, counting blood corpuscles and the spectroscopic examination of the blood; selected experiments on respiration and the stethograph; cerebral reactions and the general and special senses. At the end of the course each student devotes two or three weeks to the experimental investigation of a special subject, such as studies on the pulse; effect of anesthetics on nerves; temperature sense on the body; ergograph; electromotive phenomena in muscle; time reactions to touch, sight and hearing; effect of narcotics on frog; chest pantograph; sphygmography; stethography; plethysmograph.

From the description given, it appears unlikely that any experiments were performed on mammals, such as direct recording of blood pressure in dogs, cats, or rabbits. The first specific reference to mammalian laboratory experiments is in the annual catalogue of 1924, indicating that one-sixth of the laboratory course was devoted to mammalian experiments.

It is of much interest that the students could devote the last 2 or 3 weeks making experimental investigation of a special subject. Some 40 years later (1965), the staff of the physiology department believed that they were innovators when they organized what was designated as "in-depth" laboratory exercises which small groups of students carried out under the direction of a staff member who permitted use of his research equipment for a period of 2 or 3 weeks. Subsequently, other departments promptly offered in-depth laboratory investigations so that near the end of the first year the students had the opportunity to choose a special area for investigation from a rather large number of offerings. The cost of laboratory teaching equipment was minimized, since the administration did not have to provide numerous pieces of equipment for the entire class or a sizable portion thereof; instead, students used equipment purchased by staff members from research funds.

Professor Arthur Weysse

Dr. Weysse was the author of a zoology textbook published by Macmillan in 1904. This textbook was prepared to serve college students. At BUSM, Dr. Weysse not only taught physiology and experimental physiology (1899–1923) but also bacteriological technique for a few years (1899–1903).

Gold and Silver Medal Awards

During the years 1904–1908, two gold medals and one silver medal were awarded to BUSM for excellence of exhibits presented at national and international expositions or congresses. The exhibits winning gold medals at the Universal Exposition (Louisiana Purchase Exposition), St. Louis, in 1904, and at the Lewis and Clark Centennial Exposition, Portland, Oregon, in 1905, were prepared by collaborative efforts of Dr. A. W. Weysse, professor of experimental physiology, and Dr. W. H. Watters, professor of pathology and curator of the Museum. The material exhibited by Dr. Weysse depicted laboratory teaching equipment and results obtained by students in the physiological laboratories in the form of photographs, tracings, and so forth. Dr. Watters exhibited an impressive array of pathological specimens prepared by a gelatin process developed by him to preserve colors of tissues and organs. These excellent specimens had been prepared for study and demonstration in the museum and student classrooms.

In 1908, the first silver medal for excellence was awarded to Dr. Watters in international competition for his exhibit on TB at the International Congress on TB at Washington, D.C. (see Cat. 1909, and ff). The pathological specimens exhibited were from the Massachusetts Homeopathic Hospital Collection and were undoubtedly prepared by Dr. Watters.

Graduate Training

During the period 1907–1912 provision was made for students to earn a combined B.S.-M.D. degree in 6 years and for graduates of Boston University to enroll in the graduate school and qualify for the Ph.D. degree. The annual catalogue of 1912 is the first to announce that graduates of BUSM who had an A.B. or B.S. degree could, by meeting certain requirements, be admitted to the graduate school and pursue a program over a minimum of 2 years leading to the Ph.D. in one of the medical sciences—anatomy, bacteriology, chemistry, pathology, and physiology (pharmacology was not included until 1918). There was no mention of a concurrent program leading to the combined Ph.D.-M.D. degree. At this stage in the history of BUSM, Abraham Flexner made his detailed report on "Medical Education in the United States and Canada" published in 1911 (6). Flexner's favorable comments relating to BUSM and the Homeopathic Hospital and Dispensary are based on his evaluation made in 1909. His comments follow:

> *BUSM*—This school has an excellent building, admirably kept and well-equipped, and attractive laboratories for pathology, bacteriology, physiology, chemistry, and anatomy. There is no experimental pharmacology. It possesses a library in charge of a permanent librarian, a beautifully mounted collection of pathological material, an excellent refrigerator plant, and other features indicative of intelligent and conscientious effort.
>
> *Pathology Museum*—A small but beautifully mounted collection at Boston University is once more evidence of what conscience and intelligence will achieve despite slender financial resources.
>
> *Student Laboratories*—Nowhere in homeopathic institutions, with the exception of one or two departments at Boston University is there any evidence of progressive scientific work.
>
> Of complete homeopathic schools, Boston University, the New York Homeopathic College, and the Hahnemann of Philadelphia alone possess the equipment necessary for the effective routine teaching of the fundamental branches. None of them can employ full-time teachers to any considerable extent. But they possess fairly well-equipped laboratories in anatomy, pathology, bacteriology, and physiology, a museum showing care and intelligence, and a decent library. Boston University deserves a special commendation for what it has accomplished with its small annual income.

Salaries and Funding During Early Years

No attempt has been made to make a detailed analysis of the income and expenditures relating to BUSM. However, a few pertinent considerations applicable to early years are based on statements scattered in annual reports of the BUSM deans.

First, the major source of income was student tuition for several decades beginning in 1874. For example, in 1913–14 tuition receipts amounted to $14,163 and other income was $3,961. Most of this "other income" was not available in years prior to 1910–13, since its represents income from endowments.

Second, for many years the teaching staff received no remuneration from BUSM but derived their income from the practice of medicine. In 1879–80, for the first time, a small sum from annual income was divided among faculty members, who during the seven years of the school's existence had been "repaid only by the consciousness of the good they were doing" (BU President's 7th Annual Report, 1879–80). Even as late as 1913–14 the total salary expenditure was $6,560 compared with operation and maintenance costs of $8,966 (and cash balance of $2,598). The sum of $6,560 would not suffice to provide much salary to individuals on the administrative or teaching staff. At the turn of the century, Professors Rockwell and Weysse of the Physiology Department were probably paid a salary. Professor Weysse did not have an M.D. degree until 1907. Dr. Rockwell preferred not to practice medicine, but since he possessed some wealth (1), he may have been

generous in contributing his time and effort with minimal remuneration.

Third, before 1918–20, when BUSM was a Homeopathic School, it is unlikely that the central administrators of BU provided funds in significant amounts to BUSM, although they provided the original College Building (Building C) and the Laboratory Building (Building B) and donated the land at 80 E. Concord St. to the hospital for erection of the first Evans Hospital, which was occupied in 1912 and later purchased at a very reasonable cost by BU-BUSM about 1942 and used thereafter for teaching, research, library, and administration.

Treasurer's reports for the period 1890–1900 might reveal the source of funds required for purchase of extensive teaching equipment, especially for physiology, coincident with emphasis on laboratory teaching and the occupation of the Laboratory Building (Building B) in 1891.

Research Contributions by Dr. Frederick H. Pratt

Among the research contributions made by Dr. Pratt, who was professor and chairman of Physiology Department 1921–22, he is given credit for two important advances in physiology. In *History of Physiology* (Clio Medica, 1931, by J. F. Fulton) there is a section dealing with information concerning arteriovenous anastomosis in which the author states as follows:

> The rediscovery by F. H. Pratt (1898), Grant (1926) and Wearn (1928) of the anastomoses between the primitive Thebesian (1708) and ventricular system and the coronary capillaries of the heart has led to profound modifications in our views concerning the nutrition of this supreme organ.

This "rediscovery" by Dr. Pratt is described in an article entitled, "The nutrition of the heart through the vessels of Thebesius and the coronary veins" by F. H. Pratt, *Am. J. Physiology* 1(1), Jan. 3, 1898. The experiments described in this paper had been conducted in the laboratory of physiology at Harvard Medical School. It should be noted that Dr. Pratt received the A.B. degree from Harvard in 1896, and that in 1897, before receiving the A.M. degree in 1898, he had orally reported his findings at meetings of three societies: American Physiological Society, May, 1897 (see *Science*, June 11, 1897); Boston Society of Medical Sciences, June 1, 1897; and British Association for Advancement of Science, Toronto, Aug., 1897. The first scientific paper published by Dr. Pratt (see above) appeared in the first number of the first volume of the *American Journal of Physiology*, the organizer, first owner, and first editor of which was Dr. William T. Porter, then assistant professor of physiology at Harvard Medical School. In the published paper, Dr. Pratt states that the work had been suggested by Dr. Porter, then his teacher and later a lifetime friend. Although not so stated, it is likely that the experimental work was done while qualifying for the A.M. degree which was awarded in 1898. In the published paper, Dr. Pratt not only reviews but also adds to the anatomical evidence for anastomoses between the thebesian ventricular system and the coronary capillaries. Of even greater significance is the experimental evidence presented to indicate that the heart of several animal species receives sufficient oxygen and nutrients from the thebesian vessels to maintain cardiac function for a few hours after ligation of the coronary arteries.

The second contribution for which Dr. Pratt received special acclaim was the making of photographic records of the all-or-none response of single skeletal muscle fibers following direct stimuli of graded intensity to single muscle fibers. Thus skeletal muscle fibers obey the all-or-none law. This was done by constructing a special fine-pointed capillary pore electrode with which single muscle fibers could be stimulated. The magnitude of the contractile response of a single muscle fiber was amplified and photographically recorded by light rays reflected from a droplet of mercury in contact with a single muscle fiber. The all-or-none law had been first enunciated as applicable to heart muscle many years previously by Bowditch (1871). Unequivocal evidence had been presented to indicate that the all-or-none law was also applicable to transmission of the impulse along a nerve fiber (Adrian, 1912), and there was some evidence that it was applicable to skeletal muscle (Lucas, 1909). The clearest evidence that this law was obeyed by single cells of skeletal muscle was presented by Pratt and Eisenberger in 1919 (*Am. J. Physiol.* 49(1), 1919).

The several papers published by Dr. Pratt, some in conjunction with John P. Eisenberger, during 1917–19 are obviously classical in nature. It is clear from the publications that progress and success in the experiments depended largely on the expertise in construction and use of specialized equipment, including capillary pore electrodes 4–8 μm in diameter, which made it possible to stimulate single cells.

It appears quite likely that much of Dr. Pratt's success in the experimentation described depended on the technical and scientific contributions made by his assistant and collaborator, Mr. John P. Eisenberger. In two of the publications authored solely by Dr. Pratt he gives credit to Eisenberger, an undergraduate assistant "for aid in the construction of apparatus, and for essential contributions to the method of preparing the capillary pore" and also ". . . for furthering by many ingenious devices and patient observations the course of these studies." Eisenberger's abilities were not limited solely to technical matters but extended to biological experiments and interpretation of data as evidenced by his authorship of the rather extensive paper entitled "The differentiation of the minimal contraction in skeletal muscle" (*Am. J. Physiol.* 45: 44–56, 1917).

Do not get the impression that Dr. Pratt lacked technical and mechanical abilities. While a medical student at Harvard he worked closely with Dr. William T. Porter, who operated the Harvard Apparatus Company (then on Harvard property, before it moved to Dover, MA), which constructed equipment for physiological teaching and experimentation. Furthermore, during medical studies he spent one term in the machine shops of the Worcester Polytechnic Institute (1900–01).

It is quite possible that Dr. Pratt should be given credit for another "*first*"—the construction and effective use of capillary pore microelectrodes for stimulation of single cells. Detailed instructions for construction of such electrodes are contained in publications by Pratt and Eisenberger (1917–19). In these papers, only one reference is made to previous construction of capillary pores, and this deals solely with grinding and polishing so as to obtain a proper aperture. No reference is made to previous use of minute pore electrodes to induce biological responses in single cells.

Reorganization of BUSM (1918–1921)

During the early part of this century, BUSM ranked high among homeopathic medical schools and even among many nonhomeopathic schools. However, there was continual opposition to homeopathy, which probably accounted in large part for decrease in enrollment and loss of essential tuition monies, particularly during the second decade. This prompted the President of BU to request the faculty of BUSM to evaluate the situation. With financial aid and moral support pledged by BU, BUSM reorganized in 1918. By 1921, a substantial increase in faculty had been effected, particularly in full-time faculty. The curriculum was revised (see Ref. 2).

The reorganization of BUSM in 1918 was effected to obtain a nonsectarian designation from the Council on Medical Education of the American Medical Association by abolishing its sectarian designation as a homeopathic school (this required the establishment of courses in "old-school" therapeutics) and to offer a curriculum that was more attractive and relevant to those students who aspired to a career in the medical profession and would meet the standards established and rigorously enforced by the Council of Medical Education in order to be accredited as a class A school.

The decision was made to add 12 full-time faculty members to the basic science departments, 5 professors and 7 assistant professors or instructors. Allocation of a full-time professor was made to each of five departments, anatomy, physiology, chemistry, pharmacology, and pathology-bacteriology, and each department was allocated one or two assistant professors or instructors. By 1921, three professors were engaged to serve as chairmen of the Departments of Anatomy (Dr. Alexander S. Begg), Physiology (Dr. Frederick H. Pratt), and Pharmacology (Dr. W. L. Mendenhall) (see Refs. 2–4). In 1921, Dr. Brenton Lutz had been engaged as assistant professor of physiology, and in 1922 Dr. Leland Wyman was added to the staff as instructor. Professor F. P. Batchelder became lecturer in applied physiology in 1921 upon retirement as chairman of the Department of Physiology, a post he had held since replacing Dr. John A. Rockwell in 1902. The following obituary notice appeared in the *Boston Globe* (2/15/42):

> Dr. F. P. Batchelder, 77, professor emeritus of applied physiology at Boston University Medical School died February 14, 1942. He was born at Stafford, Conn. Dr. Batchelder received a degree of Ch. B. from Boston University Medical School in 1890 and his medical degree the following year. Establishing a practice in Boston, he served at the same time as an instructor at the school and for about 20 years from 1901 was a full professor. For many years he was connected with the Massachusetts Homeopathic Hospital. He was assistant physician at the hospital from 1894 to 1909 and since that time has been visiting physician.

According to Dr. Briggs (2), the reorganization during 1918–21 required a very substantial increase in the budget from $16,500 (salaries only) in 1918 to $83,000 in 1921, an increase of $66,500. The trustees of BU approved addition of $20,000 to the budget, but no mention is made regarding the source of the remaining $46,500. Certainly less than one-half could have been derived from tuition, even though enrollment of students had greatly increased (annual tuition and laboratory fees totaled ca. $281 in 1923, whereas the total for 1915–20 was $150–200). About 1918, the graduating class averaged about 12 in number, whereas in 1921, 61 students were registered in the freshman class.

With regard to changes in curriculum decided upon, it was stated that the number of instructional hours in the 4-year curriculum was reduced from a total of 4,690 to 4,000 hours. Following the reoganization, the hours of instruction in physiology remained the same as for 1905 and 1918, i.e., a total of ca. 320 hours (2,7); however, this was reduced to 288 hours of lecture and laboratory instruction, all of which was offered during the first year in 1923 by the new chairman, Dr. Pratt, and his staff.

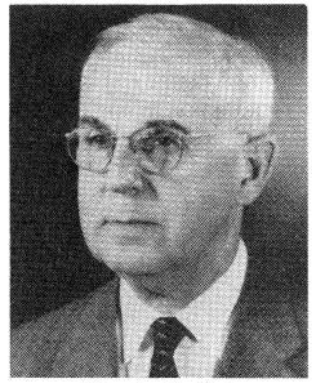
A comparison of courses of instruction offered before reorganization in 1918, with those offered in 1923 (see Annual Catalogues, 1918 and 1923) soon after reorganization and acquisition of full-time professors indicates that major changes were made in scheduling of courses and number of hours.

In 1918, a major portion of the 340 hours devoted to physiology was scheduled during the 2nd year, whereas by 1923, the number of hours had been reduced to 288 hours, all scheduled for the 2nd semester of the first year. The number of hours devoted to chemistry was drastically reduced from 384 hours, equally divided between the 1st and 2nd years, to 248 hours (80 lectures, 160 laboratory hours, and 8 quizzes), all scheduled for the 2nd semester of the first year. It appears quite certain that the shift of instructional hours in physiology and chemistry from the 2nd to the 1st year, along with reduction in total hours, was effected in order to provide increased instruction in pharmacology (total of 240 hours in 1923) and rescheduling so that it was given in the 1st semester of the 2nd year. Previously, in 1918, most of pharmacology (pharmacy, toxicology, therapeutics), except 16 hours of pharmaceutics, was given during the 3rd and 4th year of the curriculum. Laboratory experimentation in pharmacology (54 hours) had been recently initiated and was conducted in the physiological laboratories.

Obviously the content and scope of the physiology taught and the manner and methods of teaching are more important than consideration of horal numbers and annual scheduling. Unfortunately, there are no records available to yield even a smattering of information concerning content and scope of physiological lectures and laboratory instruction at different periods of time in BUSM from 1874 to 1942—no detailed schedules of lectures and laboratory experiments, no laboratory manuals, no course descriptions of value. The brief descriptions of didactic coverage of subject matter contained in annual bulletins or catalogues are inadequate and misleading because of brevity and omissions. For example, Dr. Pratt and staff mention blood and lymph in the 1923 catalogue but make no mention of cardiovascular or renal function, subject areas that were certainly covered with some emphasis.

At this point it is appropriate to comment concerning Professor Weysse, whose activities were all on the Charles River Campus of BU subsequent to 1921. Professor Weysse was not only the key person in teaching experimental physiology in BUSM for many years, but he also became active in graduate training and in research as well as teaching biology at BU. He was appointed in BUSM as instructor in experimental physiology in 1899, several years after construction of Building B, which contained the experimental labora-

Arthur W. Weysse



Brenton R. Lutz

tories. Attention has already been directed to his success in presenting a commendable laboratory course, which was mostly accomplished during 1899–1905 before he attained the rank of professor. For many years he had a dual academic appointment at BU (1905–23, prof. of experimental physiology at BUSM; 1904–39, prof. of biology and chairman of the Biology Dept. until 1927, when he was replaced by Dr. Brenton Lutz). In addition, he was chosen to be acting dean of the graduate school (1917–22) and served as dean for 11 years (1922–33).

It would be instructive to search indexes to obtain a complete bibliography of Dr. Weysse's research publications and books and to evaluate their content. Dr. George Fulton, formerly Shields Warren Professor of Biology at BU, has written (*Science* 132: 721–22, 1960) that Dr. Weysse "introduced the auscultatory method of blood pressure measurement to America in 1913." Did Weysse actually "introduce" the auscultatory method into America or was it a matter of publishing early evidence which helped to establish the reliability of the method? Dr. Fulton orally stated to the writer that Dr. Weysse had visited Russia and had probably been in contact with Korotkoff, who had first described the auscultatory method in 1905 based on interpretation of five pulse phases. I have examined two publications by Professor Weysse and B. Lutz. The first of these (*Am. J. Physiol.* 32: 427–37, 1913) consists of a careful comparison of the auscultatory blood pressure phenomenon in man with the tracing (pulse) of the Erlanger sphygmomanometer. Data obtained from 61 healthy students appear to establish two important facts. First maximum blood pressure (systolic) is coincident with the onset of the first phase of Korotkoff sounds as already claimed by foreign workers. Second, the minimum blood pressure (diastolic) is coincident with the onset of the fourth phase sounds and not with the fifth phase (cessation of sounds) as claimed by some other investigators. These data aid in establishing criteria for reliable determination of blood pressure by the auscultatory method. While these experiments were being conducted, an American investigator (possibly the first) published reports dealing with the auscultatory method (see Warfield, *Arch. Int. Med.* 10: 258, 1912; *J. Am. Med. Assoc.* 61: 1254, 1913).

The second paper published by Weysse and Lutz (*Am. J. Physiol.* 37: 330–47, 1915) concerns the determination of the normal diurnal systolic and diastolic pressures in 10 healthy male subjects using the auscultatory method, without direct comparison with any other method. Repeated determinations (30 per day) were made during waking hours. Average values were as follows: systolic 120 mmHg; diastolic 85 mmHg; pulse pressure 35 mmHg; heart rate 72 beats/min. These data may be the first published by American workers to indicate the normal values for blood pressure in young healthy adults as measured by the auscultatory method.

The teaching staff working with Dr. Pratt for the period 1921–42 appears to have been barely adequate for a medical class of 60–70 students, since Drs. Lutz (part-time at the College of Liberal Arts) and Wyman (full-time) were ranked as assistant and then associate professors throughout most of this 21-year period. In addition, Marion Reid was appointed as instructor in 1929, before the award of the Ph.D. degree in physiology in 1936, and Caroline tum Suden served as Evans Fellow at the Massachusetts Memorial Hospital and in the Physiology Department for 9 years, during which time she completed requirements for the Ph.D. degree in 1933. Drs. Reid and tum Suden were instructors during the years 1929–46 and 1940–47, respectively. Because of the lack of detailed records of teaching schedules, it is not certain that instructors Reid and tum Suden participated in didactic teaching, but it seems certain that they contributed substantially to laboratory teaching and actively pursued research projects.

Dr. Reid did teach physiology to nursing students from Boston City Hospital as indicated by a statement in her letter or resignation addressed to Dean Anderson in April, 1946: "For many years I have taught physiology to the preliminary nursing students of the Boston City Hospital and have used the facilities of the department of physiology for the demonstrations to this group."

The members of the physiology staff during 1921–42 were not rewarded by rapid promotions; on the contrary, promotions were effected only after long periods of service, as indicated by the following. Dr. Lutz served as assistant professor for 8 years (1921–29) and as associate professor in BUSM for 9 years (1930–39). During most of this time he also taught at the College of Liberal Arts. Although he was not awarded rank of professor at BUSM, the College of Liberal Arts ranked him as professor and chairman of biology from 1927–1955, the year of his retirement. Dr. Wyman served as instructor for 1 year (1922–23), assistant professor for 7 years, and associate professor for 16 years at BUSM and an additional 3 years in the Department of Biology of College of Liberal Arts before being promoted there to rank of professor in 1949.

Drs. Marion Reid and Caroline tum Suden served as instructors for 17 and 7 years, respectively, and were never promoted before leaving to assume other positions soon after Dr. Hans O. Haterius became the new chairman of the Physiology Department in 1945.

Slowness of promotion may have been due to budgetary restrictions, if one assumes that prevailing policy dictated a substantial increase in salary along with advancement in rank. There is no evidence whatsoever to suggest that failure of Drs. Lutz and Wyman to attain full professorial status was due to any deficiencies in qualifications, teaching effectiveness, or research productivity. Both accumulated impressive records of research productivity, were engaged in graduate training, and established commendable records of teaching, administration and research. Dr. Lutz became interna-

tionally known for his published research concerning the microcirculation of blood, much of which was based on the first use of the hamster cheek pouch. Dr. Wyman published numerous papers and abstracts, frequently in collaboration with Dr. tum Suden (total of 26), many of which related to functions of the adrenal glands, especially the adrenal cortex. Dr. Wyman also became well known for his contributions in sociology and anthropology.

Graduate Training: BUSM Physiology Department and BU

The Medical School was not involved in graduate training to any significant extent during the first four or five decades of its existence. However, beginning in 1912, the annual catalogues indicate that students with bachelor degrees were eligible, under specified conditions, for candidacy for the Ph.D. degree from the BU Graduate School (formerly the School of All Sciences). The annual Medical School Bulletins of early dates do not list students who were awarded graduate degrees. It is possible that the first person to earn the Ph.D. in physiology at BUSM was Dr. Brenton Lutz, who worked under the direction of Professor Weysse, and was awarded the degree in 1917. However, Dr. Weysse held appointments at BUSM and in biology at the College of Liberal Arts, so the location of Dr. Lutz's major department is uncertain. In the following year, 1918, the Ph.D. was awarded to Dr. William H. Watters during his long tenure as professor of pathology. His graduate program was probably supervised by Dr. Weysse, professor of experimental physiology, BUSM, who soon became dean of the Graduate School. Dr. Watters refers to the awarding of the degree (without meeting the German language requirement) in his "Reminiscences" (1).

In BUSM, graduate training became a major contribution of the faculty in the Divison of Medical Sciences of the graduate school in later years. It is therefore appropriate to relate facts regarding the early development of the Graduate School at Boston University.

Graduate degrees (M.A. and Ph.D.) were awarded by BU beginning with its founding and support of the School of All Sciences, the faculty of which included members of the various schools in BU. This School of All Sciences was well organized and was an innovative concept and realization of the founders of BU, being the first, or among the first, academic programs purposely organized for granting graduate degrees.

Perusal of the annual report of BU President Warren (reports 1-20, 1873-1895) reveals that full development and support of the definitive plans for a superb School of All Sciences was thwarted by failure to obtain anticipated funds. This precluded the engagement of faculty specialists who could concentrate on graduate instruction and also offer more specialized subjects. The financial strictures, which prevented more rapid growth and strength of the School of All Sciences, applied to all other units of the BU, including the Medical School, and were largely due to two events occurring in 1872, the great Boston fire and a national financial panic and depression.

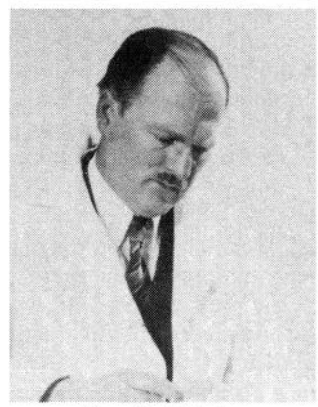
During Dr. F. H. Pratt's tenure as chairman of the Department of Physiology from 1921-42, Caroline tum Suden and Marion Reid were awarded Ph.D. degrees in 1933 and 1936, respectively.

Caroline tum Suden's supervisor was Dr. Leland Wyman. Wyman and tum Suden collaborated in writing 26 abstracts and papers between 1929 and 1945 (see biography on file in Physiology Dept.). In 1947 Dr. tum Suden was appointed assistant professor of physiology at Mount Holyoke College and in 1950 as a pharmacologist in the US Army Chemical Research and Development Laboratories. After her death in 1976 The American Physiological Society announced in the *The Physiologist* that Dr. tum Suden willed a bequest of over $100,000 to the Society, probably the largest bequest they have ever received. It was noted that her attendance and delivery of papers at annual meetings of the Society were the highlights of her career.

Marion Reid's supervisor was Dr. F. H. Pratt. They collaborated in writing several abstracts and papers (see biography on file in Physiol. Dept.). Dr. Reid held the position of assistant and then associate professor of zoology at Douglas College of Rutgers University from 1946 until her retirement in 1969. She retired to Maynard, MA, and was buried there following her death in 1975.

Instruction in physiology was carried out by Drs. Wyman, Reid, and tum Suden from the time that Dr. Pratt retired as chairman in 1942 to the appointment of Dr. Hans O. Haterius as chairman in 1945. The hours of instruction in physiology may have been curtailed during this time to a total of 210 hours (60 lectures and 150 laboratory hours), although the 1943 BUSM catalogue (1943-45) states that there was no reduction in standards or content of courses during the wartime program and the appointment of Dr. Haterius as chairman.

No graduate students were enrolled in the Physiology Department from 1942 through 1946, although there was a total of one to six registered each year in other departments in BUSM, mostly in microbiology and particularly in biochemistry. The number of graduate students enrolled in the Division of Medical Sciences of the Graduate School increased markedly following World War II because a number of war veterans were interested in graduate training and research, some of them receiving financial aid from the GI Bill in support of education; more senior faculty members were interested in providing graduate training and research experience; funds were more readily available for support of research and graduate training, major sources being the National Institutes of Health, National Science Foundation, several branches of the Armed Services, and commercial companies; and there was a strong demand for personnel with advanced scientific training, and projections indicated that this demand would continue.



Hans O. Haterius

Earl R. Loew

During the tenure of Dr. Haterius as chairman of Physiology Department (1945–48) five graduate students were enrolled and earned the Master of Arts degree. The high degree of activity in graduate training and research during the period 1947–49 can be documented by citing the papers delivered by Drs. Hegnauer and Penrod and their graduate students at the annual spring meeting in 1949 of the Federated Societies of Experimental Biology held in Detroit. Following the delivery of four papers scheduled on the same program, the session chairman spoke to the audience and highly commended the group of scientists from BUSM for their excellent research and its presentation. This praise was a satisfying reward due, in part, to the time and effort spent in rehearsal of delivery of these papers before the physiology staff members previous to the meetings (for abstracts of papers, see *Federation Proc.* 8, 1949, Penrod, Wolff, Rosenhain, Shriber, and Hegnauer).

As an example of progress in teaching medical students with emphasis on subject matter relevant to recent developments in science, commerce, and warfare was the inclusion of problems relating to the physiology of high altitude. About 1946, through connections and efforts of Dr. Maison (the chairman of pharmacology) and Drs. Hegnauer and Penrod, a high-altitude chamber was obtained from the US Army Air Force and installed at the rear of the Talbot Buildings. Dr. Penrod delivered three lectures regarding physiology of high altitude, and a laboratory exercise was carried out by Drs. Hegnauer and Penrod in which student subjects "ascended to altitude" in the chamber, and data were obtained about the physiological and psychological effects. This proved to be an instructive exercise that appealed to students.

The scope and content of lectures presented during the physiology course given during the second semester of 1946–47 can be determined by study of a bound notebook preserved in the Physiology Department. The detailed content of many of the lectures is in typewritten form, with 79 lectures on physiology presented and an additional 8 lectures devoted to statistics. Three staff members each delivered about one-third of the lectures: Dr. Haterius lectured on blood, heart and circulation, and the endocrine system; Dr. Hegnauer lectured on the autonomic and central nervous systems, muscle and nerves, the kidney, and metabolism; instructor Caroline tum Suden assisted in laboratory teaching, 1946–47. Dr. Penrod lectured on respiration, statistics, digestion, and altitude physiology.

Improvements in the Teaching Laboratory

The teaching laboratories on the third floor of Building B were used jointly by the Pharmacology Department in the first semester and by the Physiology Department in the second semester. The facilities and equipment had become antiquated and deteriorated over the years. During 1945–46, Drs. Haterius and Maison spent an extraordinary amount of time in making major improvements and innovations in the basic equipment used by students.

A bane of students and physiologists had been the use of smoked kymograph paper for recording events, followed by labeling, shellacking, and drying of the strips of smoked records. This was very inconvenient and time consuming, with distractions caused by crowding of facilities that were permeated with smoke, soot, and shellac. To initiate improvements, provisions were made to record by electrical means, thus entirely eliminating the use of smoked paper. Drs. Maison and Haterius described their new procedure in a paper on "The application of electrical recording methods to the student laboratory for physiology and pharmacology" (*J. Assoc. Am. Med. Colleges,* July, p. 3–12, 1947.

Much credit for conceiving planning, and installing equipment for electrical recording should go to Dr. Maison, who exhibited interest and ability in designing and supervising construction of mechanical devices. To facilitate electrical recording a continuous track or trolley of electric output connections was mounted on the ceiling along the entire length of the laboratory and directly above each line of work tables with extension cords that moved along the track so that the outlets could be directly over the equipment to be used. This suspension of wiring over work areas eliminated obstruction to body movements at the work table. Electrical equipment was obtained at very low cost from the US Army as war surplus. The major cost was in installation. Another requirement for the electrical recording was that the electric current had to be conducted along the writing lever and tip, and then be conducted through graphite paper (Teledeltos Paper) mounted on a metallic drum. Current flow at the writing tip "burned" a black line constituting the record. To achieve this Drs. Maison and Haterius had to engage and maintain a machinist to construct special levers and writing points used in recording from muscle levers, tambours, manometers, and so forth. These levers had to be light in weight and still conduct electricity; they were not available from commercial sources. A machinist and shop were supported by the two departments for a decade or more after 1945.

The first 75 years of physiology at BUSM have shown remarkable progress and growth and a continuing effort to meet the goals and high standards set by the founders.

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Earl R. Loew

Animal Legislation by the Congress Now Rest with the Senate

The question of Congressional legislative initiatives involving laboratory animals now rests with the Senate.

The House acted on this question at the close of the first session of the 98th Congress in late November when it passed HR 2350, the legislative renewal of National Institutes of Health (NIH) authorizations, which included amendments involving laboratory animals. The Senate is expected to act early in the second session, perhaps as early as February, in the passage of its version of the NIH renewal authorizations (S 773).

Once the Senate has acted the two bills will go to a joint House-Senate conference committee to resolve the language differences before final approval of the authorities are made by the Congress.

The House-passed bill contains four provisions that relate to research animals, while the Senate proposal has only one amendment concerning laboratory animals. However, the Senate also has a second bill, the "Improved Standards for Laboratory Animals Act" (S 657), that is being carried over from the first session and could surface during the second session.

The amendments in the House-passed bill involving laboratory animals are as follows.

- A requirement charging NIH to establish a program for the development of alternative methods, the cost of which probably will come from funds appropriated for research, inasmuch as no fiscal authorizations were included in the amendment.
- A provision requiring the Secretary of the US Department of Health and Human Services (DHHS) to promulgate by regulation guidelines for the care and treatment of laboratory animals used in NIH-funded research.
- A requirement that all NIH-supported research involving the use of animals be monitored by institutional animal care committees which are to include a veterinarian, a public member, and not more than three persons from the institution.
- A proposal for an independent 18-month study of NIH-funded programs to determine the number of animals, by species, used in research and testing during the last five years and validate the need, the increase or decrease of animals used, and the current use and status of alternative methods now available.

Other amendments approved in the House version of the NIH renewal bill call for the creation of two new institutes, one for arthritis and one for nursing, the establishment of 25 regional demonstration projects for research and prevention, and the addition of an associate director for prevention at each institute. The bill also extends all current NIH authorizations for three years.

The lone animal provision in the Senate's NIH renewal bill is the call for an independent 18-month study of animal usage and alternative methods. The only difference between the Senate's proposed study and the House study proposal is its scope. The House study is restricted to only NIH-funded animal research programs, while the Senate proposes a broader study that would include all DHHS-supported programs involving animals, and it encourages participation by institutions using animals but not receiving DHHS funds.

The Senate is expected to give consideration to this bill early in the second session now that the House has acted. One major question, however, is whether the Senate conferees will accept the other animal provisions proposed by the House when the two bills go to conference.

The future of S 773 is not as predictable. This bill, which would amend provisions of the Animal Welfare Act, has not been acted on by the Senate Committee on Agriculture, although hearings were conducted last summer by the bill's sponsor, Sen. Robert Dole (R-KS).

As a result of the hearings the bill was modified by Sen. Dole but has not been offered to the committee.

Among the amendments proposed by the bill would be the requirement that all facilities using animals would establish animal care committees that would be responsible for semiannual inspections and would add standards to provide adequate animal exercise and to minimize animal pain and distress

Also carried over to the second session will be an Administration proposal that would affect the cost for all institutions using animals for research, testing, and education. Companion bills (HR 3938 and S 1918) call for the establishment of a user's fee for the services provided by the US Department of Agriculture's Animal and Plant Health Inspection Service, including the expense of inspecting animal facilities. No action has been scheduled by either the House or the Senate agriculture committees on the Administration's proposal.

Animal Rights Group Stages Two Holiday Raids

The Animal Liberation Front struck again during the holiday season.

This year the animal rights group entered the Harbor UCLA Medical Center on Christmas Day and made off with 12 dogs that were being used for research, including five dogs with experimental pacemakers. Then the group entered a psychology laboratory at the Johns Hopkins University and took six rats that were being used in research on Alzheimer's disease.

In 1982 the Front broke into Howard University on Christmas Day and stole 28 cats and then made two break-ins at the National Naval Medical Center, taking one dog each time.

After the raid on Johns Hopkins the Front said in a prepared statement that animals are "fellow travelers on this planet" and should not be used for "painful, pointless, and repulsive" experiments. In California the group reported that all dogs were placed in homes outside the state.

William M. Samuels, CAE

Society Tour to China

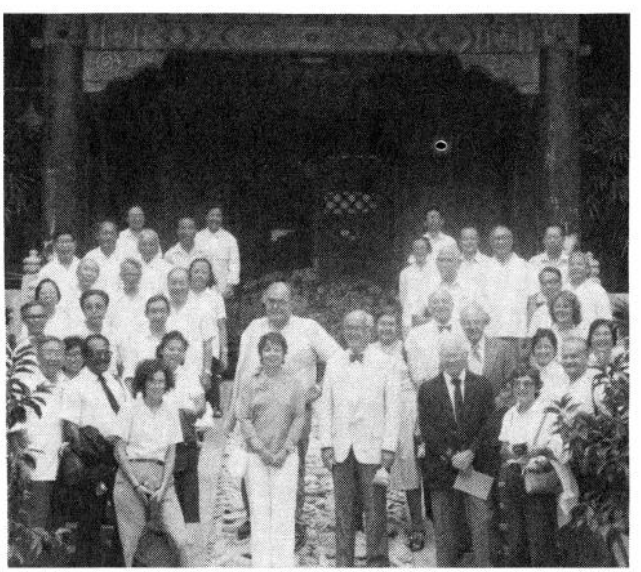
Fifteen American Physiologists and six of their spouses toured the People's Republic of China in September 1983 as a post-Congress tour following the XXIXth International Congress of Physiological Sciences in Sydney, Australia: A. P. Fishman (APS President), G. and W. C. Randall (APS Past President), H. and L. E. Farhi (APS Council), M. and O. E. Reynolds (APS Executive Secretary-Treasurer), H. Baker, A. MacDermott, H. Coleridge, J. Coleridge, K. Glendenning, M. and D. Gourley, S. D. Gray, J. and G. J. Jacobs, H. Murphy, G. and P. L. Rayford, and W. S. Rehm.

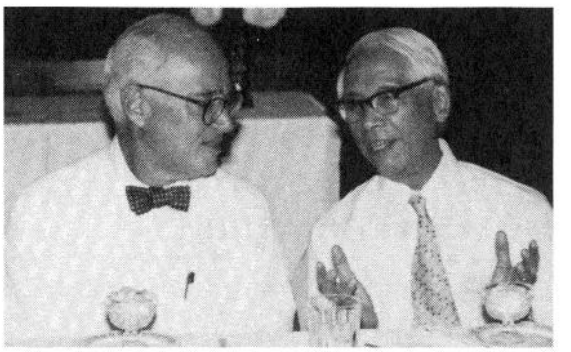
Two group meetings with Chinese Physiologists were held. The first was a tea party held in the First Medical School of Beijing (formerly Union Medical College of Peking) hosted by Professor C. C. Wang, Vice President of the Chinese Physiological Society. Among the Chinese attendees two senior physiologists, Dr. H. C. Chang and Dr. X. H. Cheng, have long been associated with American Physiologists.

After very brief introductory remarks and round the table introductions, the large group (about 50 people), on Dr. Fishman's suggestion, broke up into smaller groups according to specialty interests for scientific conversation, visits to the nearby laboratories, and general socializing. Before departure, group photographs were taken. Figure 1 was supplied by Dr. S. D. Gray.

For the remainder of the tour in Beijing several visits by individual members of the group to physiologist colleagues there supplemented the general meeting while the rest of the group was enjoying sightseeing opportunities such as visiting the Summer Palace, the Forbidden City, and the Great Wall.

On the advice of our Chinese hosts, the tour included a trip to Xian, the ancient Chinese capital before visiting Shanghai. From a standpoint of general and cultural education, this was the highlight of the tour for many of us. It included inspection of two active archeological sites, The Tomb of Emperor Qin, with the recently discovered "bodyguard" consisting of hundreds of life-size terra cotta warriors and horses, and the 6,000-year-old village of Banp. It was astonishing to see bone, flint, and pottery artifacts that to the novice looked indistinguishable from North American Indian artifacts of the pre-Columbian era. A charming evening entertainment of lute music and dancing was enjoyed by all in Xian.





In Shanghai, our American group was entertained at dinner in the Shanghai Institute of Physiology, Academy Sinica hosted by Dr. De-Pei Feng with approximately 40 Chinese Physiologists and spouses in attendance. After introductory comments and the presentation of a certificate of Honorary Membership to Dr. Feng by APS President A. P. Fishman (see accompanying comments), the small group discussions, reported as being so successful in Beijing, were suggested by the Chinese hosts.

After 3 days in Shanghai, the tour ended in Hong Kong, and members dispersed on their separate ways for return to North America.

For several years APS has been exploring the possibility of an organized visit to the Republic of China of members and officers of the Society for the purpose of improving communications. During an extended visit to NIH in 1980–81, Dr. Hsiang-Tung Chang, an APS member and Director of the Brain Research Institute of Shanghai (*The Physiologist* 24(2): 15–16, 1981), offered concrete suggestions for arranging such a visit, and communications with Dr. Feng, President of the Chinese Physiological Society, confirmed dates following the XXIXth International Congress of Physiological Sciences.

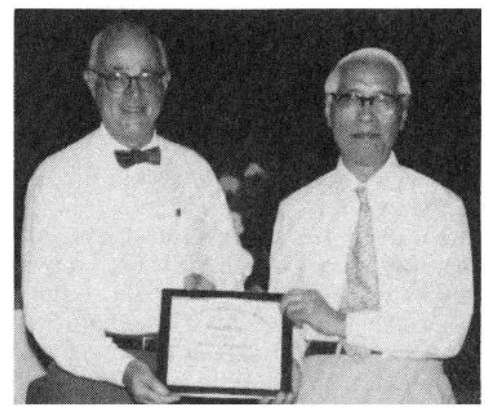
The overall organization of the China tour was remarkably good. Participants agreed that hotel facilities ranged from good to excellent. Transportation by air between cities within China was comfortable and on schedule. One representative of the Chinese International Travel Service (CITS) accompanied us throughout the trip, and an additional representative of CITS joined us in each city visited. They communicated in English uniformly well and were most conscientious in arranging maximal use of our time for exposure to Chinese culture. A private bus was provided in each city. These were roomy, comfortable, and skillfully driven. The meals were provided in restaurants throughout the tour; food was plentiful and well prepared.

O. E. Reynolds

T. P. Feng (Feng De-Pei)

Feng was born in 1907 in Linhai, Zhejiang Province, China. He studied in the School of Biology, Fudan University, in Shanghai 1922–26 and became a teaching assistant in physiology in the same university after his graduation. From 1927 to 1929 he was a research fellow in the Department of Physiology, Peking Union Medical College, working under Robert Lim on gastric secretion. In the summer of 1929, he won through competitive examination, the Tsinghua University Fellowship for studying in the United States, and in the fall of the same year, he went to Chicago University to study general physiology under Ralph Lillie and neurophysiology under Ralph Gerard, obtaining a M.Sc. degree in physiology in the Summer of 1930. After spending the summer of 1930 in Woods Hole, he went to University College London to work with A. V. Hill chiefly on the heat production of nerve and muscle and obtained his Ph.D. in 1933. During his stay in England, he had also worked with E. D. Adrian in Cambridge and J. C. Eccles in Oxford for about two months in each place. In the summer of 1933, after a brief visit to O. Meyerhof's Laboratory in Heidelberg, he came back to the United States to work for a year in Philadelphia in the then newly founded Johnson Foundation for Medical Physics whose director was Detlev Bronk. Then in 1934 he returned to China to do teaching and research in the Department of Physiology, Peking Union Medical College and stayed there until the end of 1941 when this college closed down following the outbreak of the Pacific War. During this period his pioneering work on neuromuscular transmission, appearing in a long series of papers in the *Chinese Journal of Physiology,* was well known. In 1943 he managed to leave Beijing (then called Peiping) and after a long travel through a devious route lasting more than 50 days to reach the war-time capital of China, Zhongqing, in the interior province Szechuan, and became professor of physiology in the Shanghai Medical College, which had migrated there. As the anti-Japanese War was drawing to an end in 1945, Academia Sinica planned to organize a new medical research institute and Feng was appointed its Acting Director. So at the end of 1945 he resigned his professorship in the Shanghai Medical College and began his work as an organizer of the new institute. In preparation for this new enterprise he made a trip to the United States in 1946; while there during the period 1945–47, he worked part of the time with Lorente de No in the Rockefeller Institute, at the same time visiting other laboratories and collecting equipment and books for his new institute. He returned in the summer of 1947 to Shanghai, where his new institute started in Zhongqing was now located. He was elected an academician of Academia Sinica in 1948. Following the liberation and the establishment of People's Republic of China and the formation of the Chinese Academy of Sciences, Feng's institute was incorporated into the Academy and renamed as the Institute of Physiology and Biochemistry. Feng served as director until 1958 when the institute was split into the Institute of Physiology and the Institute of Biochemistry, and he became the director of the Institute of Physiology and remains so to the present. He was elected a divisional member of the Chinese Academy of Sciences in 1955. In 1961–70, he was concurrently Vice-President of the East-China Branch of the Academy. In 1978 he became Vice-President of the Shanghai Branch of the Academy. In 1981 he was elected Vice-President of the Chinese Academy of Sciences and Director of its Division of Biological Sciences. Feng has been the chief editor of *Acta Physiologica Sinica* throughout its years of publication and is now President of the Chinese Physiological Society. He was a representative of the first, second, and third National People's Congress (NPC) and has been a member of the National Standing Committee of the Chinese People's Political Consultative Conference (CPPCC) since 1978. In spite of his heavy administrative and organizational duties Feng has never ceased to maintain an active interest in research. His current research activities are chiefly concerned with trophic relations between nerve and muscle.

Feng's scientific achievement has received international recognition. He was elected an Honorary Member of the Physiological Society (Great Britain) in 1966, of the Canadian Physiological Society in 1979, and of the Neuroscience Society (USA) in 1981. In 1981 he was awarded a Regents' Professorship by the University of California at Los Angeles and elected a Fellow of University College, London. In 1983 he was elected a member of the Council of the International Union of Physiological Sciences and an Honorary Member of the American Physiological Society.



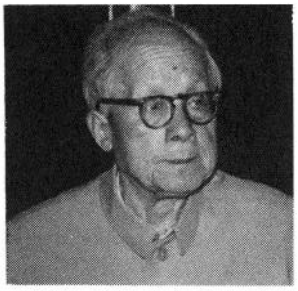
To A. P. Fishman:

It was a very great pleasure indeed to meet you and your colleagues in my institute in Shanghai, and I want to thank you once more for the great honor you did me by personally presenting to me the certificate of Honorary Membership in The American Physiological Society.

T. P. Feng
Shanghai Institute of Physiology
Academia Sinica
Shanghai, China

H. C. Chang's Sixty Years of Physiological Research

Americans are sometimes accused of lacking historical perspective; something a few centuries old seems ancient, and any delay to progress is intolerable. American physiologists are thus apt to think of their science as having been universally embraced long ago and to think that the establishment of scientific physiology would have been impossible in an atmosphere of political upheaval. It will surprise many, therefore, to learn that one of the people who introduced scientific physiology to a fourth of the world's population is still alive and active in the laboratory and that he was able to establish physiology in China in spite of hardships that we can scarcely imagine.



Hsi-Chun Chang's scientific career began 60 years ago, soon after he received his bachelor's degree from the University of Chicago and began graduate work at Rush Medical College, working simultaneously in the laboratory of A. J. Carlson. His research on the thyroid resulted in three research papers, and he received an M.D. and a Ph.D. in 1926. In 1927 he returned to his native China to do his internship at Peking Union Medical Hospital. A year later Chang joined the Department of Physiology at PUMC. This department had been modeled after the department at the University of Chicago in 1916 by Franklin Maclean, another former student of Carlson, Chang and R. K. S. Lim extended this model and for the first time introduced experimental physiology into China.

In 1932 Dr. Chang worked briefly with W. R. Hess in Zurich and then went to London to join J. H. Gaddum in Dale's laboratory. It was there that Chang and Gaddum did the work for which Chang is best known in the west: finding that the sympathetic chain contains large amounts of acetylcholine (ACh). "I had only half-year to stay in London. So I worked day and night. When the experiments on choline esterases were finished I had 3 days left to make sight-seeing of London. In a conversation with Gaddum suddenly I raised a question, saying 'John, we have analyzed ACh content of almost all kinds of animal tissues, confirming the prediction of Sir Henry Dale that ACh is not only present in plant tissue, but also in the animal tissues. But how about the sympathetic chains?' Gaddum did not answer the question, but got hold of a car. We drove immediately to the stable and fetched a sample of sympathetic chains. To our great surprise, we found it containing much more ACh than any other tissues except the human placenta. I repeated the experiments for two more days, at the expense of looking around in London, for I had to leave for Rome to attend the 14th International Physiological Congress" (Chang, personal communication).

Dr. Chang returned to PUMC in time to welcome W. B. Cannon for a half-year visit, which Chang has described in the June 1980 issue of *The Physiologist*. In 1938 Dr. Chang became acting chairman of his department. In spite of administrative duties, by 1941 he had written and co-authored more than 50 research papers. Then the Japanese invaded. Japanese soldiers occupied PUMC, locking out the staff and compelling them to find other means of earning a living. Chang returned to his hometown of Tianjin (Tientsin) and began practicing medicine with his father, who was a traditional physician.

Finally in 1948 Chang returned to PUMC as department head. The first task for the new chairman was to help two assistants clean out the garbage that the Japanese soldiers had packed to the ceilings. During the following year, as Mao Zedong was establishing The People's Republic of China, Dr. Chang published eight more papers further exploring the role of ACh. Professor Chang continued to be active in the laboratory during the next three decades while serving in a variety of administrative capacities.

During the decade 1966–1976 his research suffered another interruption no less violent than the Japanese invasion. During the "Cultural Revolution" he was "freed" from his position and barred from the laboratory. He then went to work in a mountainous region in the province of Sichuan. He was 71 years old. Within a year he became seriously ill, and while on sick leave in Beijing in 1973 he was ordered to rebuild a department in the Capitol Medical College, a branch of PUMC. This time the laboratories were empty of garbage but also empty of equipment. "I had two other assistants helping me to change the empty rooms to laboratories. At present [April 1982], the department [of Physiology, Institute of Basic Medical Sciences, Beijing] consists of 50 staff with one professor, not well equipped yet, but quite active in teaching and research. I am trying to recover it to its original size [of 80], perhaps even bigger, and enrich it with sufficient modern equipment to render better service." As if that were not enough service, Professor Chang has contributed his entire teacher's annuity to the Chinese Physiological Society, with its interest to reward the best young physiologist each year (Chang, personal communication).

In 1982 after a serious illness Dr. Chang retired as chairman of his department. Now recovered, he continues to do research. His 80th paper was recently published in the Journal of the Combination of Traditional and Western Medicine. For the past decade he has attempted to relate traditional medicine and western physiology. At age 85, Hsi-Chun Chang himself seems a living testimonial to the value of that approach.

I thank Professor Chang for providing much of the information on which this account is based, including personal letters and a copy of a manuscript recently submitted to *Perspectives in Biology and Medicine*. I also thank his son, Zhang Renji, a neurophysiologist at Peking University, for translating portions of a book published in 1983 to commemorate Chang's 60th year of research and for first bringing his father to my attention during a 6-month visit in my laboratory.

C. Leon Harris
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State University College of Arts and Science
Plattsburgh, New York 12901

APS Plenary Session
FASEB Spring Meeting
April 4, 1984

Second Annual APS Physiology in Perspective Lecture
Wednesday, April 4, 1984
Clarion Hotel (formerly Stouffers Riverfront)
St. Louis, MO

9:00 A.M. Prostacyclin—From Discovery to the Clinic
J. R. Vane, Director
Group Research and Development
The Wellcome Research Laboratories
Beckenham, Kent, UK

9:45 A.M. APS Business Meeting
A. P. Fishman, President
American Physiological Society

10:30 A.M.-1:30 P.M.
Free Time to Visit the Exhibits
(APS Symposia and Sessionswill *not* be scheduled during this period)

Immediately after the lecture, the American Physiological Society will hold its Business Meeting. No scientific sessions other than Dr. Vane's lecture will be scheduled by APS for Wednesday morning. Following the Business Meeting, the remainder of the morning will be left free for visiting the exhibits at the Convention Center.

APS Centennial Collection of Physiological Instruments and Equipment

As part of the Centennial Celebration of the American Physiological Society, we would like to form a small collection of physiological instruments and equipment to be placed on exhibit at the Centennial meeting and afterward at the APS headquarters. Instruments, devices, and methods useful in the detection, measurement, and recording of physiological functions have played a major role in the progress of physiology over the last century. Some of these instruments have been borrowed from other disciplines, but many have been specially invented by physiologists and have opened up whole new areas of research. At times a simple gadget, later relegated to the trashcan, played an important role. There are presently no available collections of this material. Even the most familiar laboratory instruments of a generation ago are not being saved. A Centennial Collection, it is hoped, will serve as a tangible reminder of past achievements.

We are eager to hear from members of the Society or any other readers of possible available contributions. If you have such equipment that you would be willing to donate to the APS Centennial Collection, please send us a description of it. Or if you have items of historical value that you do not wish to donate but would be willing to loan, or know where such items may be located, please let us know. We would especially welcome examples of the most common laboratory instruments of the past.

Please write to M. C. Shelesnyak, Task Force Director, Centennial Celebration Committee.

Section on the History of Physiology Organizational Meeting

An organizational meeting of the Section on the History of Physiology will be held at 4:45 P.M., Tuesday, April 3, 1984, in the Mississippi Room of the Clarion Hotel, St. Louis. At that time, the Section will be discussed and officers elected.

Young Investigator Prize in Environmental Physiology

The Environmental, Thermal and Exercise Physiology Section of APS will again present the annual prize for outstanding research in environmental physiology by a graduate student. The prize includes a cash award of $200, which will be presented at the Temperature Regulation Dinner during FASEB week. To be eligible for the award, the graduate student must have presented or will present a paper at the 1983 Fall or 1984 Spring Meeting and must be the first author on the published abstract. Either a typewritten copy of the presentation or a manuscript related to the research should be submitted by March 15 to Dr. E. R. Nadel, John B. Pierce Foundation Laboratory, 290 Congress Ave., New Haven, CT 06519. The Award Committee will notify all applicants of its decision by March 30.

Previous prize winners are B. Pinshow, Duke University (1975); M. Maron, University of California, Santa Barbara (1976); L. K. Vaughn, University of Michigan (1977); D. E. Lemons, Portland State University (1978); J. M. Steffan, University of New Mexico (1979); M. O'Donnell, University of California, Davis (1980); R. Moalli, Brown University (1981); K. J. A. Davies, University of California, Berkeley (1982); and N. Rousch, Mayo Medical School (1983).

Comparative Physiology Section

The Comparative Physiology Section of the American Physiological Society held a business meeting August 23, 1983 in the Honolulu Room of the Sheraton Waikiki in Honolulu, HI. Because there was not a quorum present, official business could not be conducted. However, discussion of the possibility of implementing an award for a graduate student presentation at APS Fall Meetings was discussed. Those present agreed that this matter should be placed on the agenda of the next meeting of this section to be held in Lexington, KY.

It was announced that Dr. Robert Blake Reeves, Dept. of Physiology, School of Medicine, State University of New York, Buffalo, NY, was elected as the new counsellor for our section for a three-year term expiring in 1986. The officers for the coming year are H. T. Hammel, Chairman (term expires in 1984); M. R. Fedde, Secretary (term expires in 1984); D. C. Jackson, Program Advisory Committee, APS (term expires in 1984); and S. C. Wood, Counsellor (term expires in 1985); and R. B. Reeves, Counsellor (term expires in 1986).

M. R. Fedde, Secretary

APS Fall Meeting

August 26–31, 1984, Lexington, KY

The 35th Annual Fall Meeting of the American Physiological Society will be held August 26–31, 1984 in Lexington, KY. Registration will be located in the Lexington Center and will open at 2:00 P.M. on Sunday, August 26. Scientific Sessions—slide sessions, poster sessions, symposia, and tutorial lectures—will be scheduled in the Lexington Center and Hyatt Regency Hotel on Tuesday, August 28, through noon Friday, August 31. The APS Refresher Course will be held on Monday, August 27. The call for papers and general information will be mailed to members March 1, 1984. *Deadline for receipt of abstracts:* May 14, 1984.

Symposia and Special Sessions (tentative titles)

Loaded breathing: load compensation and respiratory sensation

Current topics in neuroendocrine control of reproduction

Quantitative approaches to the study of cardiovascular regulation

Workshop: physiologist's approach to age-dependent changes in function

Workshop: integrative approaches to physiology education

Intrarenal hemodynamics

Alteration in microcirculatory function during hypertension

Vasoactive agents in control of the mesenteric circulation

Neural control of renal function

Chronophysiology and athletic performance

Thermoregulation in the elderly

In addition to symposia, a series of tutorial lectures will be programmed. A special lecture titled, "Experiences of a blue grass physiologist in space," will be presented by Astronaut Story F. Musgrave.

Refresher Course

Determinants of oxygen uptake during exercise, organized by Daniel Richardson and Bryant Stanford

Bowditch Lecture

Glycoprotein hormone genes: hormonal regulation of expression, by William W. Chin

For further information: APS Fall Meeting Office, 9650 Rockville Pike, Bethesda, MD 20814. Telephone 301/530-7010.

Future Meetings

1984

FASEB Annual Meeting — April 1–6, St. Louis
*APS "Fall" Meeting — Aug. 26–31, Lexington

1985

FASEB Annual Meeting — Apr 21–26, Anaheim
*APS "Fall" Meeting — Aug 4–9, Buffalo

1986

FASEB Annual Meeting — Apr 13–18, St. Louis
IUPS Congress — July 12–20, Vancouver, Canada

*Campus meeting

APS Publications

Sensory Processes, a New Handbook

The Society begins 1984 with the completion of a new *Handbook of Physiology* in the section on the Nervous System. *Sensory Processes* has been edited by Ian Darian-Smith; John M. Brookhart and Vernon B. Mountcastle are the Section Editors.

Publication of *Sensory Processes* occurs at a time when our knowledge of these processes is increasing at a furious rate. It is expected that this volume will provide a platform from which the reader may assess the achievements of the last 20 years, appreciate the problems that now challenge the investigator, and, not least, experience some of the exhilaration of participating in the chase.

Since 1960 there has been quite remarkable progress in our understanding of the neural events mediating the detection, discrimination, and recognition of objects around us. The most apparent developments have been technical. One such advance—recording from peripheral and central neurons while the experimental subject performs a specific sensory task—has been a singularly important step forward. A second has been the development of powerful new anatomical methods for tracing axon projections and connections, for analyzing synaptic organization, and for mapping focal changes in metabolic activity within the central nervous system. The importance of these technical advances has been that their use highlights aspects of brain function that were not previously accessible for study and as a result were somewhat neglected. For example, whether a monkey subject is attending to a particular stimulus while responses to that stimulus are being recorded in a cortical neuron suddenly assumes key importance. The investigator must become inquisitive about the behavioral state of the subject if the responses of that cell are to be understood, a circumstance necessarily ignored in earlier studies of similar neurons in the anesthetized animal. Similarly, the new knowledge of thalamocortical connections obtained by using axon tracing techniques has evoked a whole catalogue of new questions about the functions of the separate thalamic nuclei and the various cortical subfields to which they are linked. What is also apparent is that answers to these questions are likely to be obtained only by carefully planned application of combinations of the new tools available to the investigator.

The plan of *Sensory Processes* is straightforward. After an outline of the historical perspectives of sensory research, sections of the volume are concerned with the measurement of sensory performance in man and experimental animals, with the structural organization of sensory systems, and then with a systematic survey of current knowledge of the neural bases of vision, hearing, somatic sensibility, and the chemical senses. Included in this survey are chapters on the perception of the body in space and on the functional asymmetry of the human cerebrum.

Members of the American Physiological Society may order *Sensory Processes* from the Subscription Office of the Society, 9650 Rockville Pike, Bethesda, MD 20814. The price to members is $220 for this 1244-page, 2-part volume, with 636 figures (nonmember price $275).

What's in a Name?

By all criteria, the *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology* is an unqualified success. But not all who are responsible for its success are satisfied with its name.

The biggest hang-up is with the designation "applied." Many believe that this is a derogatory term that does not sit well with the interests of the Journal, colleagues in fundamental science, or promotions committees. Others, notably those who have grown up scientifically with the Journal, recognize in the title, *Journal of Applied Physiology*, a label of quality, distinction, and tradition. Contributing to the uncertainty is the qualifer, "Respiratory, Environmental and Exercise Physiology," a project of the last decade and part of the master plan for defining boundaries for the journals of the American Physiological Society.

Even the founding fathers of the *Journal of Applied Physiology* were a bit shaky about their choice of title. The following is a verbatim recount of the original editorial as it appeared in Volume 1 of the *Journal of Applied Physiology,* July 1, 1948.

> This is the first number of a new Journal intended to serve the needs of one of the fields of physiology. That field is designated as "applied" physiology and perhaps requires some delimitation. The application of the facts, principles, laws, methods and technics of physiology, the mother of the biological sciences, is not at all new, but is as old as the science itself. In connection with this Journal the term "applied" will broadly connote human physiology, with particular emphasis on man in relation to his environment and the adaptations his physiologic mechanisms show in response to the many and varied stresses imposed by man's environments. The terms "stress" and "environment" will also be interpreted broadly to include work, exercise, industrial, military, climatic, nutritional and even social and economic factors, as well as those that seem, in the shadow of our present lack of knowledge at least, to arise from within the body itself. For example, physiological aspects of heredity, of aging and the aging process, and of metabolism will come within the scope of this Journal. At the present time the stresses imposed upon man's mechanisms for homeostasis by climate, altitude, temperature and work are receiving much intensive study by physiologists and the need of another medium for the publication of such studies is urgent. Research emphasis, however, may shift in the future and the scope of the JOURNAL OF APPLIED PHYSIOLOGY has purposely been set along broad lines to accommodate wide shifts in interest. The term "physiology" will be interpreted rather strictly in delimiting the field of the Journal.
>
> Over the past forty years the number of medical and biological journals has increased a hundred-fold and still continues to increase. It would seem to be incumbent upon those responsible for inaugurating a new journal to set forth the reasons which, in their opinion, justify calling upon the groups served to support the publication both by the contribution of articles, and by subscription and use.
>
> The extension and diversification of physiological publication has caused the urge for the establishment of new specialized journals or the restriction in scope on existing ones. It becomes inexpedient for a journal to diversify its contents more and more in an attempt to serve an expanding subject completely. A far greater variety of subjects must be included than are of direct interest to individual workers or to specialized laboratories. This increased the cost of those articles that are desired to such an extent that an individual's subscription support of a journal may be discontinued and dependence placed upon libraries and other repositories. This is not altogether desirable and to a considerable extent may be offset by the formation of specialized organs of publication, provided they serve a field that has a considerable permanent interest and a large body of active workers.
>
> Additional journals, hence, appear to be an inevitable consequence of the expansion and specialization of a field. New scientific knowledge gained from research is sterile without some degree of publication; with limited or restricted publication it fails to achieve its highest objectives. Indeed, unless it is published in media that are accessible to scientists throughout the world, it may become essentially lost and useless. Much of modern physiological research demands enormous expenditures for complex apparatus, instruments, equipment and laboratories, for highly trained technical and professional personnel, and for planning and administration. Few would question the justification of large expenditures of public and private funds for such support. The essential corollary, that of adequate facilities for publication, has not been implemented to the same extent. Yet it is as essential to the increase and diffusion of scientific knowledge as are the researches that originate that knowledge.
>
> The AMERICAN JOURNAL OF PHYSIOLOGY, founded in 1898 and now in its one hundred and fifty-fourth volume, exemplifies the amazing development, extension and specialization of physiological research during that time. This journal currently publishes more than 350 papers a year covering almost all aspects of experimental physiology. This is only a part of the total yearly increment. The JOURNAL OF APPLIED PHYSIOLOGY has accordingly been initiated by the American Physiological Society in order to better serve the growing and more specialized needs of this field of research. It is intended to complement and not to compete with the older journal of the Society. The policies of each journal will be kept in close har-

mony with those of the other through the agency of the Board of Publication Trustees. The Editorial Board is charged with the responsibility of carrying out these policies and of maintaining high standards of quality. It is planned to add an advisory editorial board of outstanding physiologists outside of North America to encourage the contribution of research papers from abroad. (*July 1948*)

In recent years, requests to reconsider the title of the Journal have grown louder and more numerous. But it is still not clear either to the Editor or the Publications Committee that most of those who write for the Journal, or those who read it, are sufficiently unhappy with the title to advocate change. Or if change were advocated, what the new title should be.

In the attempt to sample the views of contributors and readers, a questionnaire has been distributed to the members of the American Physiological Society who have expressed interest in the fields of Respiratory, Cardiovascular, Environmental, Thermal, or Exercise Physiology. However, one problem with this approach is that even though these members are contributors to, and readers of, the Journal, they do not represent the full constituency.

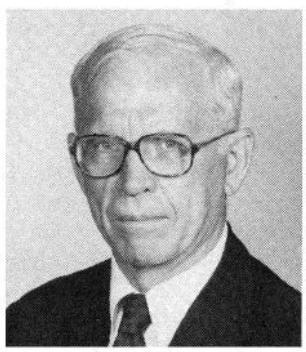
The purpose of this essay is threefold: *1*) to alert all interested in the Journal that a poll about its title is underway, *2*) to invite others than those in the fields identified above to obtain a ballot and vote, and *3*) to indicate that letters are open for expressions of opinion concerning the advisability of changing the title of *The Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*.

Your vote and views will be helpful in settling this troublesome issue.

A.P. Fishman, Editor
Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology

Lasker Award for Basic Medical Research

Neurobiologists **Vernon Mountcastle**, of Johns Hopkins, and **Eric Kandel**, of Columbia, are the recipients of an Albert Lasker Award for their work on the cellular basis for memory and learning.



Dr. Mountcastle, Section Editor of the *Handbook of Physiology, Nervous System,* and Chief Editor (1962–1964) and editorial board member of the *Journal of Neurophysiology,* was cited for his work with monkeys. Over many years, he studied monkeys as they reacted to the environment and performed tasks. From his findings he developed the concept of the brain as more of an integrative unit than hierarchical.

Dr. Kandel, Volume Editor of the *Handbook of Physiology, Cellular Biology of Neurons*, and long-time editorial board member of the *Journal of Neurophysiology*, studied the giant brain cells of the sea snail *Aplysia* and showed how they control behavior and memory.

APS-USNC/IUPS Travel Grant Program List of Awardees XXIX IUPS Congress, Sydney Aug. 28–Sep. 3, 1983

Travel awards to the XXIX International Congress of Physiological Sciences in Sydney, Australia, were made possible by grants from various government and nongovernment sources as well as from the APS (see *The Physiologist,* August 1983). Most of the APS Funds ($44,000) came from donations (as a voluntary assessment) from members of the Society, enabling the APS not only to support the travel of younger scientists, but also to demonstrate to other funding agencies the level of members' commitment to international communication. Such a show of interest was certainly an important factor in the favorable response to APS proposals requesting grant monies from funding agencies.

P. Adams
K. Albertine
M. Andressen
J. Ardell
W. McD. Armstrong
H. Baker
R. Balaban
D. Barfuss
D. Baylor
S. Baylor
P.D. Bell
M.V.L. Bennett
J. Bhattacharya
M. Blaustein
J. Bonventre
T. Bucher
D.W. Bullock
R. Bunger
D. Busija
T. Butler
W. Calder
J.H. Caldwell
R. Capranica
M. Castellini
J.R.G. Challis
V. Chan-Palay
H.-J.J. Chen
S.B. Clark
H. Coleridge
J. Coleridge
H. Cooke
A. Coquelin
L. Cornett
D. Costa
J. Cowan
N.P. Curthoys
B. D'Aoust
R. Davis
G. DiBona
S.J. Dodgson
D. Dorsa
S.P. Duckles
B.R. Duling
D. Eckberg
F. Eldridge
W.R. Ellington
M. Feder
J. Feldman
C. Fischette
J. Fisher
J.A. Fishman
M.J. Fregly
P. Gander
G. Gebber
R. Gerrity
J. Gilmore
M. Gold
C. Goodman
D. Granger
C. Greer
W.L. Grovum
J. Gutknecht
J.E. Hall
J.S. Handler
M. Heath
C.M. Heesch
N. Heglund
K. Herrup
B.T. Hinton
T. Hintze
M.P. Hlastala
A.R. Hohimer
U. Hopfer
A.J. Hudspeth
A.C. Huntley
M. Jacobson
K. Johnson
S. Kayar
S.A. Kempson
T.G. Kennedy
T. Kildruff
B. Klitzman
G. Kooyman
U. Kopp
L.M. Kow
P. Kvietys
S. Lahiri
A. Lechner
P. Leung
S.F. Lewis
J.K.J. Li
M. Lieberman
J. Maderdrut
K. Magleby
A. Malik
T.A. McCalden
J.E. Mckenzie
M. McLaughlin
M. Menaker
M. Meredith
J.A. Michael
M. Milanick
D. Millhorn
R. Moore
M. Moore-Ede
R. Murphy
R.A. North
W. North
J. O'Neill
C.L. Ortiz
E. Pagani
J.R. Pappenheimer
T.W. Pearson
J. Potter
T. Pritchard
D. Ramsay
R. Reale
T. Reese
A.A. Rovick
E.H. Sage
F. Sant'Ambrogio
M. Schneider
R. Shapiro
A.P. Shepherd
D. Shepro
J.M. Shick
G. Sieck
W.L. Silver
S. Sims
J.J. Singer
D. Smith
P. Smith
R.J. Solaro
S. Soltoff
G. Somjen
A.P.Somlyo
A.V. Somlyo
J.J. Spitzer
J. Spitzer
D. Spray
K. Spring
N. Staub
B. Stein
B.T. Stokes
D. Stone
A. Stuart
B. Sweeney
R. Tallman
T. Thrasher
J. Trubatch
H. Valtin
A. van den Pol
F. Vargas
J. Vergara
D. Warshaw
R.C. Webb
A. Weber
M.J. Welsh
J. West
J.T. Williams
T. Williams
C. Wood
J. Wood
E. Wright
J. Zengel

Harry G. Armstrong (1899–1983)

The Society lost an illustrious member with the death in San Antonio, Texas, February 5, 1983, of Harry G. Armstrong. He was 12 days short of his 84th birthday. In 1934, Malcolm C. Grow, Surgeon General of what was then called the US Army Air Force, selected a young flight surgeon Harry G. Armstrong, to create the Aero Medical Laboratory at Wright Field, Dayton, Ohio. The concept was that high-altitude combat flight being made possible by engineering research at Wright Field required parallel research on the physiological problems of high altitude confronting the crew of such aircraft.

In organizing the new laboratory, Armstrong sought the advice of Cecil and Philip Drinker, Harvard School of Public Health. Based on their advice he ordered a duplicate of their altitude chamber and hired their young physiologist, John W. Heim.

Armstrong had six busy years of research and writing. The first edition of his classic, *Principles and Practice of Aviation Medicine*, was published in 1939. He received many honors, and from 1949 to 1954 as Major General he served as USAF Surgeon General. More details of his military career are related in *Aviation, Space, and Environmental Medicine* (April 1983).

He was elected to membership in the society in 1948; he treasured that honor. In that year, F. G. Hall and I were invited by Armstrong to take part in a Panel Meeting on Aero Medical Problems of Space flight at Randolph Field where "Maj. Gen. Armstrong" was Commandant of the School of Aviation Medicine. The next year Hall and I and many colleagues were guests of the Air Force on a flight to Lima to take part in a symposium arranged by Profs. Carlos Monge M. and Alberto Hurtado on the "Biology of High Altitude." More detail about these adventures are found in my story about F. G. Hall [*Physiologist* 22(2): 8–21, 1979].

D. Bruce Dill

Henry Longstreet Taylor (1912–1983)

Henry Longstreet Taylor died in St. Paul, Minnesota, on November 10,1983. He will be remembered for his outstanding contributions to human physiology and to the epidemiology and prevention of coronary heart disease.

Henry Taylor graduated from Harvard College in 1935. Later, while attending Harvard Medical School, he participated in research at the Harvard Fatigue Laboratory, where he began his long association with Ancel Keys. Keys persuaded Taylor to come to the University of Minnesota, where he received his Ph.D. degree in Physiology in 1941 and joined the faculty in the Laboratory of Physiological Hygiene. He held a joint appointment with the Department of Physiology and its graduate faculty under the chairmanship of Maurice Visscher and later Eugene Grimm.

Henry Taylor was an outstanding scientist and scholar, best known for landmark studies in human circulation and metabolism. His research over four decades spanned human cardiovascular physiology, temperature regulation, metabolism and nutrition, aging, and cardiovascular epidemiology.

In the late 1930's and early 1940's, he investigated the chemistry of bone and the chemical and colligative properties of human plasma and plasma expanders. He was a major contributor to the landmark Minnesota study on the biology of human starvation (1). This work influenced those concerned with the recovery of semi-starved victims of World War II and led to important insights on how changes in nutrition and body composition alter organ function and a variety of regulatory processes.

Henry Taylor's studies of human work performance, the adjustments of the cardiovascular system, and the regulation of water and electrolyte metabolism are classics. Another outgrowth was the establishment, for investigative and evaluative purposes, of an *objective* measurement of cardiovascular function by a procedure known as the "Maximal Oxygen Uptake Test" (2). This measurement, as devised by Taylor and his colleagues, provides a means for physiologists to assess the functional capacity of the cardiovascular system in normal subjects and also provides functional reference for other physiological changes. It also became the foundation for the clinical exercise test now employed by cardiologists throughout the world. Henry Taylor recognized the importance of providing a sound quantitative basis for making physiological comparisons between individuals. More significantly, he recognized that the functional capacity of a biological system is an essential specification in any description of how that system operates. This kind of clear logic underlay all his research. His investigation of the physiological significance of the maximal oxygen uptake contributed to understanding the cardiovascular and metabolic factors that ultimately limit the ability to consume oxygen and stimulated key research in this area both in the United States and abroad.

Henry Taylor understood the inseparability of many functions and was one of the first to undertake a multisystems approach in the study of human temperature regulation. He identified some of the cardiovascular problems associated with thermal stress. He examined the manner in which thermal stress influences energy metabolism and the regulation of body fluids and electrolytes and, conversely, how metabolism and fluid balance alter temperature regulation. He also contributed to the development of techniques for the simultaneous measurement of plasma volume, total body water, and extracellular and intracellular fluid volume. He published a classic study concerning mechanisms of acclimatization to heat (3). He contributed much to our current understanding of how the circulation adjusts to chronic high loads [the subject of his excellent chapter with Francisco Grande in the *Handbook of Physiology* (4)] and to chronic inactivity (bed rest). He explored the utility of the ballistocardiograph for the evaluation of cardiac function and participated with Dr. Carleton Chapman in some of the first studies of the dye dilution technique for the determination of cardiac output, along with a critical evaluation of the foreign gas method of Grollman (5).

During the 1960's and 1970's, the scope of Henry Taylor's research broadened to even more difficult biological and clinical problems. Eventually Henry began to explore some of the biological problems

associated with aging and ultimately he pioneered in cardiovascular epidemiology (6). With his distinguished Minnesota colleagues, he produced the pivotal work on the role of physical activity in the development and prevention of coronary artery disease.

Underlying Henry Taylor's uniquely broad view of human physiology and his scholarship was a thorough grasp of technology and its limitations. His scientific perspective was unique. Scientists throughout the world sought his advice and benefited from his wisdom and expertise. Throughout his career he served on many national and international committees and review bodies, including long service to the American Heart Association Research Committee and Councils on Epidemiology and National Institutes of Health Study Section.

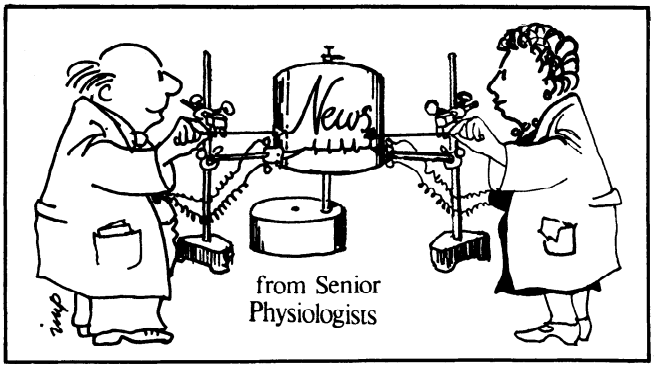
Henry Taylor will be greatly missed by all his colleagues over the world. His former students feel an enormous loss. We are deeply grateful for his dedicated tutelage, his unfailing loyalty, his complete honesty, and for all he demanded of us. We remember him with affection.

References

1. Keys, A., J. Brozek, A. Henschel, O. Mickelsen, and H. L. Taylor. *The Biology of Human Starvation*. Minneapolis, MN: Univ. of Minnesota Press, 1950, 2 volumes, 1385 pp.
2. Taylor, H. L., E. R. Buskirk, and A. Henschel. Maximal oxygen intake as an objective measure of cardiorespiratory performance. *J. Appl. Physiol.* 8: 73–80, 1955.
3. Taylor, H. L., A. Henschel, and A. Keys. Cardiovascular adjustment of man in rest and work during exposure to dry heat. *Am. J. Physiol.* 139: 583–591, 1943.
4. Grande, F., and H. L. Taylor. Adaptive changes in the heart, vessels and patterns of control under chronically high loads. In: *Handbook of Physiology. Circulation*. Washington, DC: Am. Physiol. Soc., 1965, sect. 2, vol. VIII, chapt. 74, p. 2615–2677.
5. Chapman, C. B., H. L. Taylor, C. Borden, R. B. Ebert, and A. Keys. Simultaneous determinations of the resting arterovenous oxygen difference by the acetylene and direct Fick methods. *J. Clin. Invest.* 29: 651–659, 1950.

L. B. Rowell
H. Blackburn
E. Buskirk

[Donations in memory of Dr. Taylor may be made to the Henry Longstreet Taylor Graduate Student Fund and sent to Dr. Henry Blackburn, Director, Laboratory of Physiological Hygiene, University of Minnesota, 611 Beacon St., SE, Minneapolis, MN 55455.]



Ragnar Granit to Arthur B. Otis:

In my previous reply to Ladd Prosser (*Physiologist* 25: 428, 1982), I mentioned my intention to withdraw from active science (born in 1900). I have since published a memoir (*Hur det kom sig*, Norstedts, Stockholm, 1983) with a subtitle, translated "How it came about," remembering research and motivations. Against a personal background of changing environments the book presents people and places from the author's participation in the early revival period of the neurosciences that was based on the advent of the amplifier. I have also written a number of obituaries (Yngve Zotterman, Hugo Theorell, Ulf von Euler, and Eric Kugelberg), and at present I am responding to an invitation from The Royal Society to write an obituary of my old friend Keffer Hartline for its series *Biographical Memoirs*. I note with pleasure that Floyd Ratliff has promised to be its co-author. Finally, I have served as chairman of the Natural Science Commission of the international Italo-Swiss Balzan Foundation. Its prizes have for some time been Swiss Franc 250.000 and are likely to remain at that level. This year it goes to Ernst Mayr of Harvard.

Eriksbergsgatan 14
S-11430 Stockholm, Sweden

Roy O. Greep to Arthur:

To whomever reads these columns with interest as I do I feel called upon to respond to *ABO's* request for a response. The new phase in existence that has arrived for myself and my wife is our introduction to hospital care. After better than three-quarters of a century with nary an admission for illness we have, in turnabouts that naturally loomed as prospective reruns of the "one-hoss shay," totaled five admissions over the past years.Thanks to the marvels of modern medicine and surgery and third-party payments we're still largely intact.

I get some mental exercise in part by conferring with Dr. Patricia Donahoe's research group at the Massachusetts General Hospital anent Mullerian inhibitory substance, writing an occasional historical item, and managing the annual Laurentian Hormone Conference.

Physical exercise comes in the form of gardening, grounds-keeping, and fueling the fireplace. No jogging. One of the advantages of growing old is that one can get tired doing nothing.

I have also served as a visiting professor at the St. George's University Medical School on the Island of Grenada each year over the past five years and observed the social, political, economic, and military developments at first hand. It would be easy to expatiate, but let me comment only that sampling the situation there was an object lesson on life without liberty and freedom, i.e., no newspaper, sealed lips, don't ask questions, and censored news amidst an unending drumbeat of propaganda over airways touted as Radio Free Grenada. It was remindful of the proverbial value placed on water after the well had gone dry.

135 Oak St.
Foxboro, MA 02035

Tsai-Fan Yu to Arthur:

I am glad to report to you that I am still the first one to unlock the door in the morning and the last one to leave the lab and office in the evening. So long as I am in perfect health, I am continuing my activities in the study of gout and its related diseases. Although I have published more than 200 papers, each question answered reveals more questions. The summit is yet to be reached.

The Mount Sinai Medical Center
New York, NY 10029

J. H. Bateman to E. B. Brown:

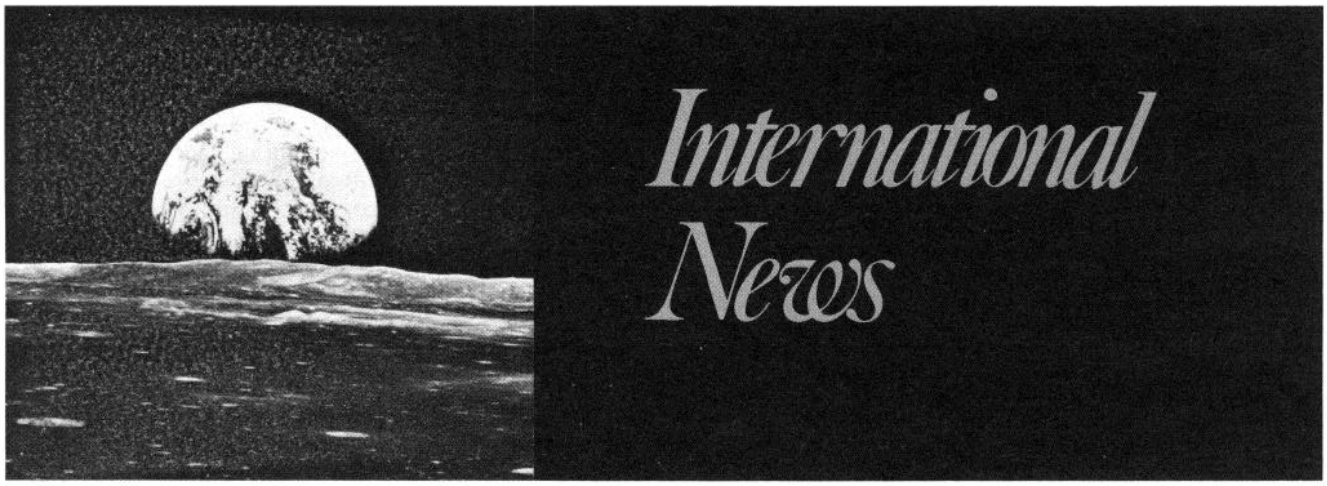
For the past couple of years I have been with Ted Grant's dielectrics group at Queen Elizabeth College (University of London). My honorary appointment there has enabled me to resume work along the lines that interested me in the 1940's, when I spent several short periods with Larry Oncley in E. J. Cohn's laboratory at Harvard and with Potapenko at Cal Tech. After having to spread myself too thin for my own good in the intervening years, it is fun to have once more that feeling of learning less and less about less and less, as the saying ought to go. As for words of wisdom for younger colleagues, I must echo Keffer Hartline, "Never take advice." With more pomp and less wit I'd add that wisdom nullifies itself in the uttering!

6 Colney Hatch La.
Muswell Hill
London N10 1DU, UK

George F. Koepf to Roy Greep:

I am still working but in an administrative capacity at the Medical Foundation of Buffalo. It seems that my research days are over. None-the-less in my capacity of President-Treasurer I still rub elbows with an elite corp of 35 research oriented scientists. This in itself is a stimulating and rewarding experience although second best to real benchwork. The Medical Foundation of Buffalo is a nonprofit independent institute founded in 1956 for the purpose of doing basic research in endocrinology. Our strengths involve research in estrogen biosynthesis and in determining the molecular structure of hormones. The X-ray crystallography department of the Foundation ranks among the largest in the world. Aside from my work, my wife and I enjoy gardening and fishing each summer at our island home on Georgian Bay, Ontario. I also still manage to stagger around a golf course once or twice a week. During the remainder of the year we live in the center of Buffalo, close to the laboratories of the Foundation. We enjoy the wonderful climate as well as the cultural and recreational activities of Western New York State.

Medical Foundation of Buffalo, Inc.
Research Laboratories
Buffalo, NY 14203-1196



1984 IUPS Regional Meeting

The 1984 Regional Meeting of the International Union of Physiological Sciences will be held in Jerusalem, Israel, August 26–31, 1984. The meeting will be hosted by the Israel Physiological and Pharmal Pharmacological Society. Scientific sessions will take place in parallel during 3½ days: the mornings and afternoons of Monday 27th, Tuesday 28th, Thursday 30th, and the morning of Friday 31st of August. Wednesday 29th is scheduled for research and teaching demonstrations, and for tours and visits to the various research institutions throughout the country.

The scientific program is composed of Symposia and free communications:

I. Respiratory Physiology—Respiratory mucociliary epithelia, J.G. Widdicombe (UK); Oxygen toxicity, L. Farhi (USA); Pulmonary adaptation, D. Flenly (UK).

II. Cardiovascular and General Physiology—Calcium currents in cardiac muscles, W. Trautwein (W. Germany); endogenous regulators of the Na-K pump, M.P. Blaustein (USA).

III. Kidney and Epithelial Physiology—Cellular Metabolism and kidney function, K. Thurau (W. Germany); Transcellular transport mechanisms in epithelia, G. Giebisch (USA); Hormonal receptors and action in kidney, H.E. de Wardener (UK).

IV. Gastrointestinal Tract Physiology—Water and Electrolyte transport in human intestine, L. Turnberg (UK) and D. Rachmilevitz (Israel); Gastrointestinal hormones and pancreatic secretion, J.F. Rehfeld (Denmark); Intestinal lipid absorption, R. Dekelbaum (Israel); Salivary gland physiology, O.H. Petersen (UK) and A. Selinger (Israel).

V. Endocrinology—Hormone receptors in health and disease, P. de Myets (Belgium); Mechanisms of Hormone Release, H. B. Pollard (USA); Prostaglandin involvement in the endocrine system, B. Samuelson (Sweden).

VI. Neuroendocrinology—Adrenocortical hormones—brain relationships, L. Martini (Italy) and S. Feldman (Israel); Sex hormones—brain interaction, W. Wuttke (W. Germany) and U. Zor (Israel); Mechanisms of secretion and action of oxytocin and vasopressin, J. J. Dreifuss (Switzerland) and I. Chowers (Israel); Reproductive endocrinology, D. Baird (UK) and Y. Koch (Israel).

VII. Cellular Neurobiology—Channels in biological membranes, B. Sackman (W. Germany) and Y. Palti (Israel); Calcium and neuronal function; B. Katz (UK) and R. Rahamimoff (Israel); Membrane receptors, G. Burnstock (UK) and Y. Lass (Israel).

VIII. Developmental Neurobiology and Brain Repair—Brain repair, A. Bjorklund (Sweden) and M. Schwartz (Israel); Neuronal death, J.K.S. Jansen (Norway) and M. Spira (Israel); Cell lineages differentiation and system assembly, J. G. Nicholls (Switzerland/USA) and I. Parnas (Israel).

IX. Central Nervous System—Intrinsic organization of the neocortex, O. Creutzfeld (W. Germany); Models of epileptogenesis, U. Heimemann (W. Germany); Central control of movement.

X. Sensory Mechanisms of the Nervous System—The physiological basis of sensory evoked potentials, H. Sohmer (Israel); Neuroethology of spatial localization, J. M. Camhi (Israel); Senstory processing in alert animals and man, S. Hochstein (Israel).

XI. Environmental Physiology—A three-day symposium on Life in stressful environments (Physiological adaption): desert, climate, space, aquatic and fassorial, S. Samueloff (Israel) and A. Shkolnic (Israel).

XII. The Teaching of Physiology

Travel Awards Third International Congress on Cell Biology, Japan, August 1984

Limited travel funds are available for the Third International Congress on Cell Biology, Tokyo, Japan, August 26–31, 1984. Awards of up to $1,000 will be made on a competitive basis, as selected by a committee. The awards will be made primarily to younger scientists and scientists participating in the Congress by invitation. Applications must be accompanied by and will be scored on the basis of *1*) curriculum vita and bibliography, including date of receipt of highest earned degree; *2*) evidence of Congress participation, e.g., letter of invitation to serve as lecturer, chairperson, discussant, etc.; *3*) abstract of Congress presentation, limited to 250 words; and *4*) resume of purpose of the trip other than attending the Congress, e.g., other meetings, satellite symposia, lab visits, collaborations, etc. There will be a limited number of similar awards made to graduate students, who should apply under the same guidelines. *Address for applications:* Dr. Richard S. Young, Executive Officer, American Society for Cell Biology, 9650 Rockville Pike, Bethesda, MD 20814. *Deadline:* 28 May 1984. Notification will be in early July.

Fondation de Physiopathologie Professeur Lucien Dautrebande Prize

The Fondation de Physiopathologie Professeur Lucient Dautrebande will award its next prize during 1985 for work on human or animal clinical physiopathology, preferably having therapeutic implications. Deadline: December 15, 1984, *Information:* Dr. J. Stalport, Président, 35 Cahussée de Liége, 5200 Huy, Belgium.

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Hospital Practice January 1984

'Physiology in Medicine': Introductory Comments

Editorial

With this issue, HOSPITAL PRACTICE begins a collaborative editorial venture with the American Physiological Society: monthly feature articles on "Physiology in Medicine." In the past, these were a successful ongoing program of the APS, appearing in *The New England Journal of Medicine*. The present incarnation of "Physiology in Medicine" arose as a consequence of dialogue between the editors of HOSPITAL PRACTICE and the Publications Committee of the American Physiological Society. Both perceived clearly the need for a series of articles that translated fundamental observations in modern physiology into rational frames of reference for understanding disease processes and therapeutic strategies and that analyzed succinctly the pathophysiologic derangements in disease states in terms of fundamental physiologic processes.

The ground rules for the collaborative publication are straightforward. We intend to present groups of articles dealing with various themes in one or another of the major organ systems, e.g., the heart, gastrointestinal tract, hematopoietic system, and central nervous system. Each series, consisting of approximately six articles, will focus on a general topic rather than on an entire spectrum of disorders. Each article, although related closely to other articles in a given series, will also be complete in itself.

This editorial is by Thomas E. Andreoli, who will serve as the editor of "Physiology in Medicine" for HOSPITAL PRACTICE *and the American Physiological Society. Dr. Andreoli is Professor and Chairman of the Department of Internal Medicine at the University of Texas Health Science Center, Houston, and former editor of the* American Journal of Physiology: Renal, Fluid and Electrolyte Physiology.

The First Series

The first series, organized by Dr. K. Lance Gould—who also will serve as associate editor of the "Physiology in Medicine" series—focuses on dynamic imaging of the coronary circulation in health and disease, coupled with an evaluation of the relation of cardiac performance to cardiac metabolism. In the introductory article, "Metabolic and Functional Cardiovascular Imaging," which appears on page 115 of this issue, Drs. Gould and Richard A. Goldstein provide a general overview of the newer aspects of dynamic metabolic and functional imaging of cardiovascular disease and the applicability of these sophisticated technologies to the practice of clinical medicine.

Stated briefly, the general subject of the first six articles is cardiovascular disease—more specifically, ischemic heart disease. Emphasis will be on the application of dynamic imaging techniques in the diagnosis and treatment of occlusive disease of the coronary arteries; the significance of platelet-endothelial interactions in the pathogenesis of atherosclerosis and of acute myocardial infarction; and the application of new therapeutic strategies, including intracoronary thrombolytic therapy with streptokinase, in the early treatment of acute myocardial infarction.

In the initial article, Drs. Gould and Goldstein provide a general frame of reference for understanding the potential significance of dynamic functional imaging of

Editorial

the coronary circulation and of myocardial function. The authors describe some of the well-recognized characteristics of conventional imaging techniques, such as arteriography, and contrast them with the kinds of information to be obtained by positron emission tomography (PET) scanning with multiple isotopes.

The second article in the series, by Drs. Nizar Mullani and Gould, will describe some of the characteristics of PET scanners in detail, their potential applicability and limitations, and some of the general concepts for "modeling" the coronary circulation and myocardial function by PET scanning. The authors also will discuss the feasibility of developing low-cost PET scanners for use in small hospitals.

The use of intracoronary thrombolytic therapy as an acute interventional device for reperfusion in patients with acute myocardial infarction will be the subject of the third article, by Drs. Richard W. Smalling and Gould. The authors also will discuss potential agents that might permit immediate intravenous thrombolytic therapy in patients with acute myocardial infarction.

The fourth article, by Drs. Richard Kirkeeide, Mullani, and Gould, will describe the physiology and pathophysiology of stenotic lesions of the coronary arteries and ways in which pharmacologic maneuvers—notably coronary vasodilation—coupled with PET scanning allow one to assess the functional significance of relatively mild degrees of coronary artery stenosis. The authors also will consider the ways in which such imaging techniques might be useful for studying the reversibility of coronary artery stenotic lesions detected in their early stages.

Consideration of the physiology of endothelial-platelet interactions, with respect to the pathogenesis of both atherosclerosis and acute myocardial infarction, will be provided by Dr. Laurence Harker in the fifth article.

Finally, in the concluding article of the series, Dr. Heinrich Taegtmeyer will provide a context for analyzing the biochemical basis of myocardial metabolism and will relate these metabolic processes to "metabolic" imaging of the myocardium with PET scanning techniques.

The Second Series

The second series of "Physiology in Medicine" articles in HOSPITAL PRACTICE, written by leading investigators at various institutions, will deal with themes relating to the gastrointestinal tract. Some will focus particularly on the liver, with emphasis on the mechanisms of ascites formation in hepatic disease and on the characteristics of hepatic coma. Closely related will be a discussion of the effects of prolonged alcohol ingestion not only on hepatic function but also on gonadal function. There will be two other articles also dealing with derangement of the hepatobiliary tree: one on the pathogenesis of gallstones and another on congenital jaundice.

Finally, two articles in the gastrointestinal series will target the alimentary tract. One will discuss the pathogenesis of peptic ulcer and the evolution of therapeutic strategies for this disease. The second will discuss the mechanisms of secretory diarrhea and the formulation of therapeutic strategies for diarrheal disorders based on a rapidly expanding body of information about the mechanisms of salt and water transport in the small intestine and colon. A subsequent series of articles will deal with the hematopoietic system.

I am enthusiastic about participating in this exciting joint editorial venture of HOSPITAL PRACTICE and the APS. If we succeed in translating physiologic precepts into rational guideposts for understanding clinical disorders, our purposes will have been well served.

THOMAS E. ANDREOLI, M.D.

Cardiovascular Imaging Metabolic and Functional

K. LANCE GOULD *and* RICHARD A. GOLDSTEIN *University of Texas Health Science Center, Houston*

Physiology in Medicine commences in HOSPITAL PRACTICE with six articles on dynamic imaging of the coronary circulation. The series begins with an overview of such new and noninvasive modalities as nuclear magnetic resonance and positron imaging, which provide metabolic as well as anatomic images of cardiac function.

Historically, the treatment of cardiovascular disease has been conservative, focusing on management of complications without altering the course of the basic pathology. A powerful pharmacopoeia that has evolved in recent years has had a major impact on cardiovascular therapy; however, it remains directed primarily at complications. The major changes that we foresee in cardiology involve several fundamentally different approaches to cardiovascular diagnosis and therapy, which have only recently become feasible through advances in imaging technology.

The first of these main changes relates to the early diagnosis of mild coronary artery disease in asymptomatic individuals some years before onset of clinical manifestations associated with the severely calcified, advanced atheroma. On the basis of primate experimentation and limited human studies, early coronary disease appears to be reversible. Early diagnosis thus becomes an essential, integral part of optimal therapy aimed at regression, an approach we call diagnostic therapeutics.

Noninvasive tests for coronary artery disease have not proved adequate to detect reliably or to quantify even advanced clinical disease—much less early, mild asymptomatic disease. The best noninvasive test, involving exercise stress with thallium perfusion imaging, has a sensitivity and specificity of approximately 85% in selected patient populations with a 35% to 60% prevalence of coronary artery disease. When applied to asymptomatic populations, a positive exercise thallium test will have only a 10% probability of correctly identifying patients with anatomically significant coronary artery disease. Thus, the technique is not adequate for screening purposes.

Accurate, reliable, noninvasive diagnosis and quantification of early coronary artery disease in humans would permit us to test in prospective, carefully controlled fashion the hypothesis that early human coronary atherosclerosis is reversible.

Dr. Gould is Professor and Director, and Dr. Goldstein is Assistant Professor, Division of Cardiology, Department of Medicine and the Graduate School of Biomedical Sciences, University of Texas Health Science Center at Houston. *The research described in this article was carried out as a joint collaborative project with the Clayton Foundation for Research.*

In cooperation with the American Physiological Association

Positron imaging of myocardial perfusion during maximal pharmacologic coronary vasodilation is capable of identifying 47% diameter coronary narrowing in dogs. This technique is based on the observation that at maximal coronary vasodilation, there is a relative maldistribution of perfusion between myocardium supplied by a stenotic coronary artery and other parts of the same heart supplied by normal arteries. Positron imaging after coronary vasodilation has exhibited a diagnostic sensitivity of 97% and specificity of 100% in a small group of patients with symptomatic coronary artery disease. These results await confirmation in larger numbers of patients. The technique's accuracy in asymptomatic subjects remains to be tested.

We use the term "selective prevention" for an approach involving potential early detection and specific pharmacologic therapy in individuals with documented disease that is not clinically manifest. This approach is, therefore, quite different from that of current large epidemiologic studies or clinical trials. Such studies to date involve groups of people in whom the prevalence of disease is unknown; they lack any basis in specific knowledge of silent coronary artery disease and its progression in individuals; and they utilize death or new cardiovascular events as end points. These end points may be poorly related to anatomic progression of coronary stenosis; instead, mortality or new cardiovascular events may be more directly related to other factors, such as arrhythmias, left ventricular function, catecholamine levels, clotting tendencies, platelet activity, or other cardiovascular behavior only indirectly associated with the progression of atheroma.

There are many examples of problems arising from the design protocols of epidemiologic or clinical trials. A number of major studies on antiplatelet therapy have been designed to test the hypothesis that platelets play a role in coronary artery disease. None has demonstrated significant benefits, but the study results are difficult to interpret. Comparable controversy characterizes many studies on the effects of lipid control on mortality attributed to coronary artery disease. Such controversy arises from the difficulties of interpreting the results of large epidemiologic studies without knowledge of the presence, severity, and progression of coronary disease in specific individuals in both control and treated groups. The Multiple Risk Factor Intervention Trial (MRFIT) exemplifies this problem.

The incidence of cardiac deaths and coronary events in the United States may have begun to fall significantly before changes in dietary, exercise, or smoking habits were widely adopted; thus, it is not clear that this decline in cardiovascular disease is the consequence of risk-factor control. Our doubts are reinforced by the fact that a Spartan life, even as exemplified in marathoners, does not prevent clinically significant coronary atherosclerosis. On the other hand, smoking appears to be a well-documented risk factor for coronary disease, with a decline in risk upon cessation of smoking. These observations all point up the necessity of concurrent controls in intervention trials.

However, there are notable exceptions to the generally negative findings of epidemiologic studies on dietary management. The Finnish Mental Hospital Study, utilizing dietary control to lower cholesterol in a tightly circumscribed population, demonstrated a substantial reduction in subsequent mortality from coronary heart disease. The recent Western Electric Study in Chicago also demonstrated that dietary lipid control may be beneficial.

We believe there are three major criteria for a successful intervention study to document the reversal of coronary atherosclerosis in humans, all based on advanced imaging technology. These are

1) early diagnosis of anatomically mild disease in asymptomatic individuals by accurate noninvasive techniques, which are repeated during treatment to demonstrate regression or progression of disease—with each patient acting as his or her own control in comparison to corresponding untreated subjects;

2) definitive end points for anatomic progression or regression, established by quantitative coronary angiography or accurate quantitative perfusion imaging, or both, thus avoiding sole reliance on indirect indices, such as new cardiac events or mortality;

3) randomly assigned treated and untreated control groups followed using the same techniques—with hard, specific anatomic or physiologic end points established to demonstrate a difference in rates of progression between the groups.

This goal of selective prevention or diagnostic therapeutics is feasible not only because of technologic advances in imaging but also because of a better understanding of coronary phys-

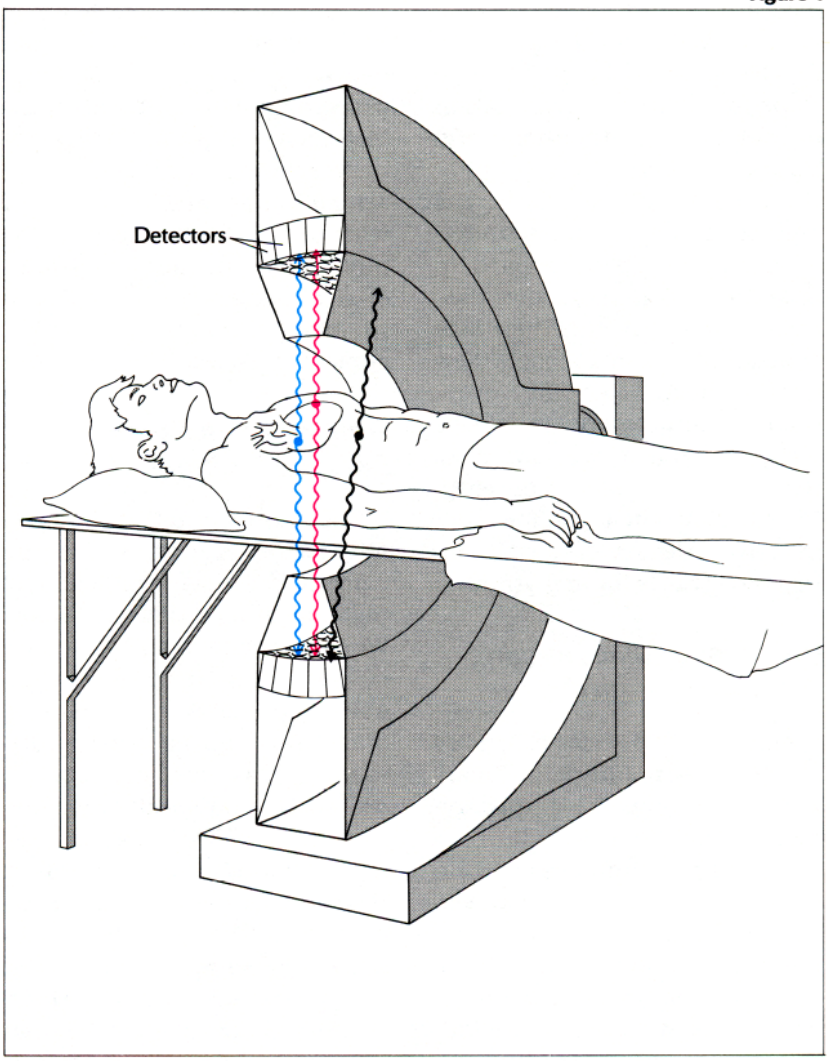
iology and how it may be manipulated for diagnostic or therapeutic purposes. The approach to "cure" in coronary artery disease has broadened its focus on lipid biochemistry and epidemiology to include, in addition, the pharmacologic manipulation of the coronary circulation and clinical application of high imaging technology applied on a significant scale. Technology may assume an even greater role in diagnostic therapeutics if balloon angioplasty becomes a sufficiently effective and safe modality for asymptomatic, early coronary stenoses, which are still soft enough to be amenable to such procedures. Mechanical dilation is particularly appealing when coronary stenoses become more severe as a result of medial cell proliferation despite resolution of atheroma on antilipid therapy, as recently demonstrated in primates.

Man as the Experimental Model

The second fundamentally new approach to diagnostic therapeutics that we foresee in cardiology involves the noninvasive, quantitative measurement of myocardial flow, metabolism, and function in man as the experimental model. Much of our understanding of pathophysiology and abnormal metabolism in cardiovascular disease is derived from animal experimentation. This knowledge has been refined to such an extent for much of cardiovascular disease that further major advances will depend on the direct study of humans by noninvasive quantitative imaging. Thus, given the limits of extrapolation from animal to human models, clinical investigation has entered a phase in which man is to a certain extent the only appropriate model or subject for the study of abnormal physiology and metabolism as well as for the evaluation of new therapeutic interventions.

For example, several primate studies have demonstrated reversibility of coronary atherosclerosis, but the phenomenon has not been verified in humans. The pathophysiology of ischemic myocardial injury and recovery with reperfusion has been well described in the experimental literature. However,

Figure 1



Schematic shows the basic physics of positron imaging. On decay of its parent atom, a positron, or beta particle, is emitted and travels several millimeters in tissue before annihilating with a negative electron present in tissue. In the process of the positron-electron annihilation, two high-energy photons of 511 kev each are emitted in exactly opposite directions. With a coincidence detection system one decay can be recorded only when the pair of photons (color) strike the two paired detectors. Decays from outside the path (black) are electronically discarded, since only one of the detectors records a photon without a coincident detection. This electronic collimation is more efficient than mechanical collimation using lead shields. In addition, the difference in time of flight for the photons in a pair to reach the detectors can be used to approximate the annihilation site.

because of major species differences, our understanding of clinical ischemia remains profoundly limited. What is reversible injury? How is it measured? How should we treat it? The development of chronic atherosclerosis with unpredictable degrees of collateralization makes it very difficult to study or reach conclusions about salvage of myocardium in patients with acute myocardial infarction. Definitive information will have to come from clinical investigation of metabolism, function, and myocardial perfusion by quantitative imaging. Similarly, the metabolic abnormalities underlying cardiomyopathies, particularly those seen in diabetes mellitus, remain undefined for lack of adequate animal models. New imaging technology may eventually permit regional metabolic mapping and visualization of regional myocardial beta-receptor distribution to define noninvasively the regional risk and metabolic basis for arrhythmias.

Invasive Cardiac Imaging—the Gold Standard

Although this series of articles emphasizes noninvasive imaging, coronary arteriography remains the gold standard to which other techniques are compared. As used now, however, the procedure has several limitations. Interpretation of coronary arteriograms is complicated by marked observer variability. Because we use relative percent diameter narrowing as the only measure of severity, we ignore other critical geometric characteristics of stenoses, such as length, absolute diameter, multiple lesions in series, and eccentric lesions. It is therefore difficult to know from visual interpretation whether the stenosis has changed with therapy. Only computerized quantitative analysis of coronary arteriograms, as recently validated experimentally, can provide an adequate standard for determining stenosis severity. Accordingly, one article in this series (by R. Kirkeeide) will describe the state of the art in quantitative analysis of arteriograms, whereby pressure-flow characteristics of coronary stenoses can be predicted by automated computer processing. This material on the technology of quantitative coronary arteriography will be presented simply and conceptually within the framework of the physiology and fluid dynamics of arterial stenoses, as observed in vivo, along with practical clinical applications.

Standard Noninvasive Imaging Techniques

Thallium perfusion imaging with the standard gamma camera is a useful indicator of regional myocardial perfusion. When combined with exercise stress testing, it provides valuable information for the clinical diagnosis of coronary artery disease, with, as noted previously, a sensitivity and specificity of approximately 85% in patients being evaluated for chest pain. However, as mentioned, the accuracy of this test diminishes when applied to a population of asymptomatic patients. Furthermore, thallium imaging does not reliably localize the coronary artery involved or identify one-, two-, or three-vessel disease.

Because of these limitations in accuracy, there is a trade-off or reciprocal relation between diagnostic sensitivity and specificity, i.e., as thallium images are "over-read," a greater proportion of tests are read as positive. However, that increase in the identification of disease is counterbalanced by the greater proportion of tests that will be interpreted as positive in the absence of anatomic disease. A noninvasive imaging technique must have a sensitivity and a specificity of approximately 98% to be satisfactory as a screening method for coronary artery disease in asymptomatic patients.

Radionuclide ventriculography is done with a standard gamma camera used to image the left ventricular blood pool after red cells have been labeled with technetium-99m pertechnetate. Gated blood pool imaging, therefore, provides a measure of the pump function of the left ventricle. The global ejection fraction, which is the percent of blood in the left ventricle at the end of diastole that is ejected during the subsequent systole, is highly accurate and reproducible. It provides a valuable measure of cardiac function, which is of great importance in the diagnosis and management of congestive failure, coronary artery disease, hypertensive heart disease, cardiomyopathies, and most other heart disease as well. An abnormal ejection fraction (below 50%) is also prognostic of decreased survival.

For example, approximately 30% of patients admitted to our hospital with classic congestive heart failure have normal systolic pump function with normal ejection fraction but have pulmonary edema because of diastolic dysfunction. Such patients have a stiff, noncompliant left ventricle associated with elevated end-diastolic pressure and secondary pulmonary edema. Inotropic agents in these circumstances may

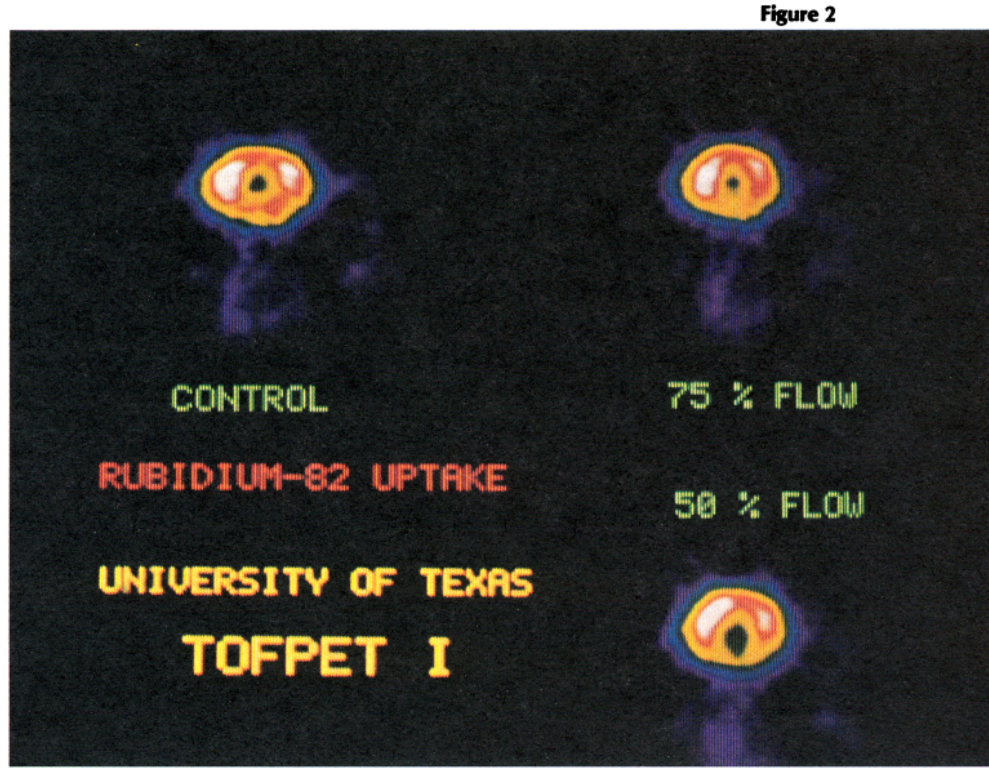
worsen the compliance of the ventricle and exacerbate the condition or prevent improvement. Diuretics and calcium blockers or beta blockers are indicated.

For purposes of diagnosing coronary artery disease, radionuclide ventriculography also has been combined with exercise stress testing. Normally, the ejection fraction rises with exercise, but in the presence of coronary artery disease the ejection fraction falls. The sensitivity of this test for diagnosing coronary artery disease is fairly high (90% or greater) but a positive test is nonspecific (specificity, approximately 50%). The proportion of false-positive results associated with this technique severely limits its value.

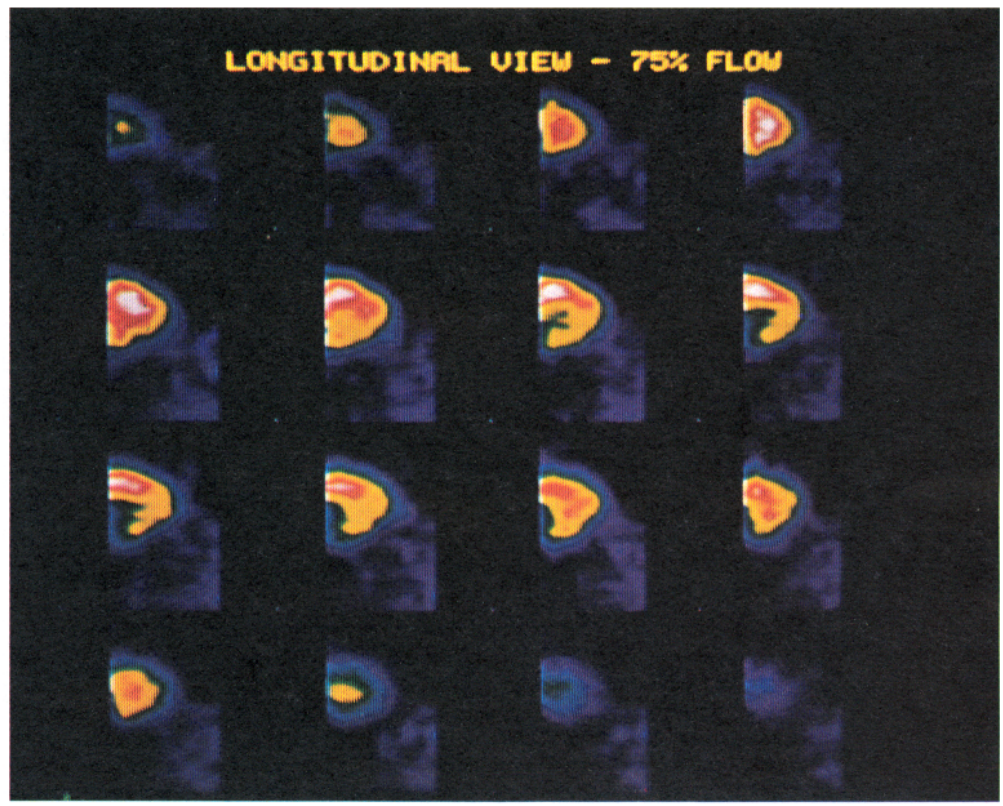
Finally, radionuclide ventriculography is useful for visualizing regional contractile abnormalities characteristic of regional myocardial ischemia, as opposed to the global decrease in function characteristic of cardiomyopathies or hypertensive heart disease. The assessment of regional ventricular function, however, remains visual and qualitative, since there are no generally accepted techniques for quantitative regional analysis of gated blood pool images for regional ventricular function. There are several inherent problems with a standard gamma camera for planar imaging of either a thallium- or a technetium-labeled blood pool. First, overlap of the front of the heart over the back of the heart obscures count information from the posterior myocardium and prevents visualization of subendocardial perfusion, which is initially affected by proximal coro-

(continued on page 123)

Figure 2



In cross-sectional tomographs (above), anterior myocardium is at the top, LV free wall on left, ventricular septum on right, and posterior myocardium at bottom. In longitudinal sections, anterior wall is at top, posterior LV wall at lower half, apex on right, and AV ring on left. Posterior wall shows obvious decrease in perfusion, even with small (25%) reduction to 75% of maximal flow.



(from page 119)

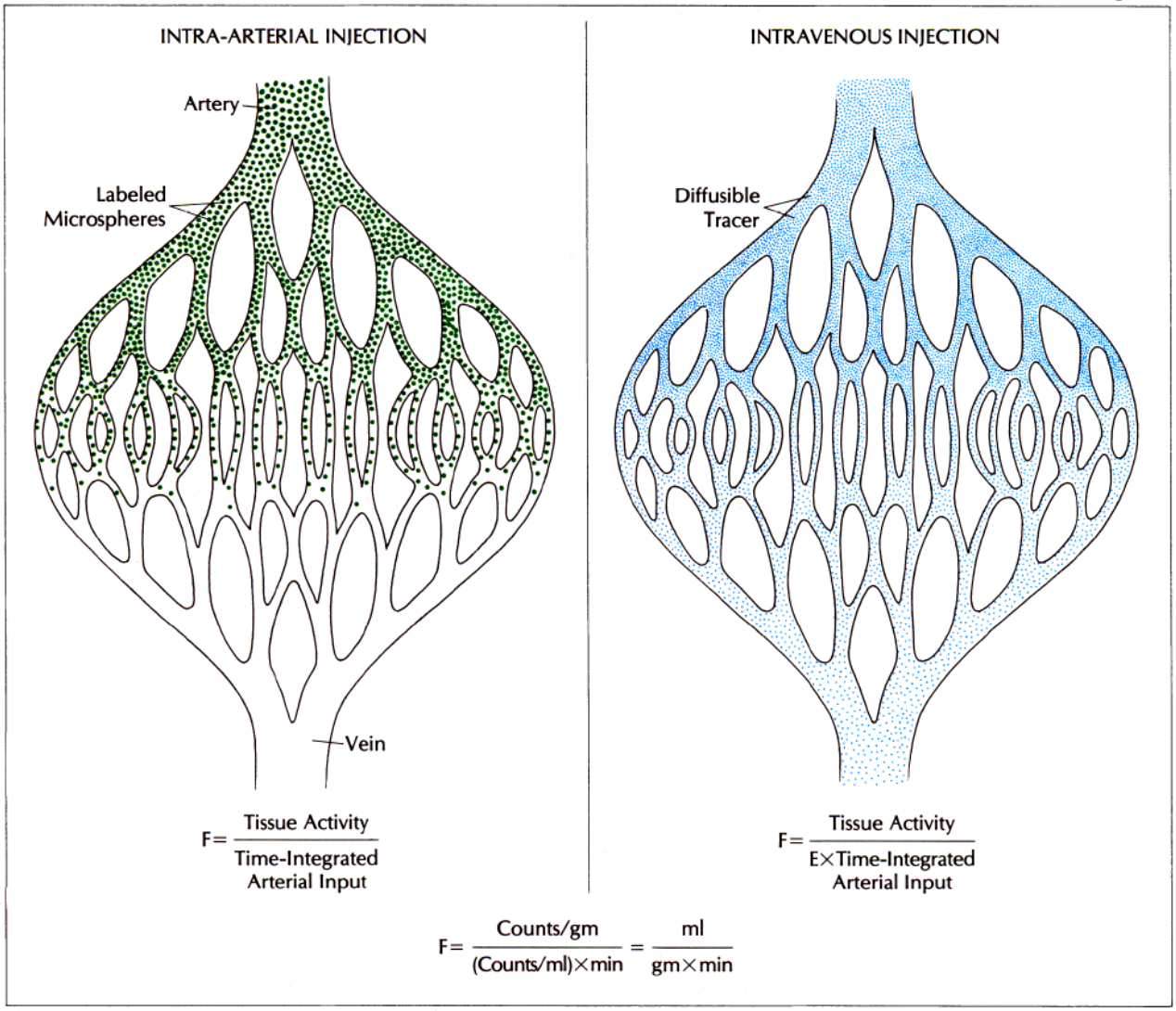
nary artery stenosis. In addition, accumulation of background activity throughout the lung diminishes the contrast between the heart and surrounding tissues. Further, the resolution of the camera decreases with depth of field, and activity is attenuated as it passes through tissue en route to the gamma camera.

Newer Imaging Technology

Digital subtraction angiography (DSA) is a technique in which x-ray information is converted to digital form for computerized manipulation in order to enhance contrast, subtract nonspecific background shadows, and quantitatively analyze image densities. For the heart, an ECG signal is obtained along with the video data for temporal localization of each image, so that the time sequence of images and rate changes can be recorded.

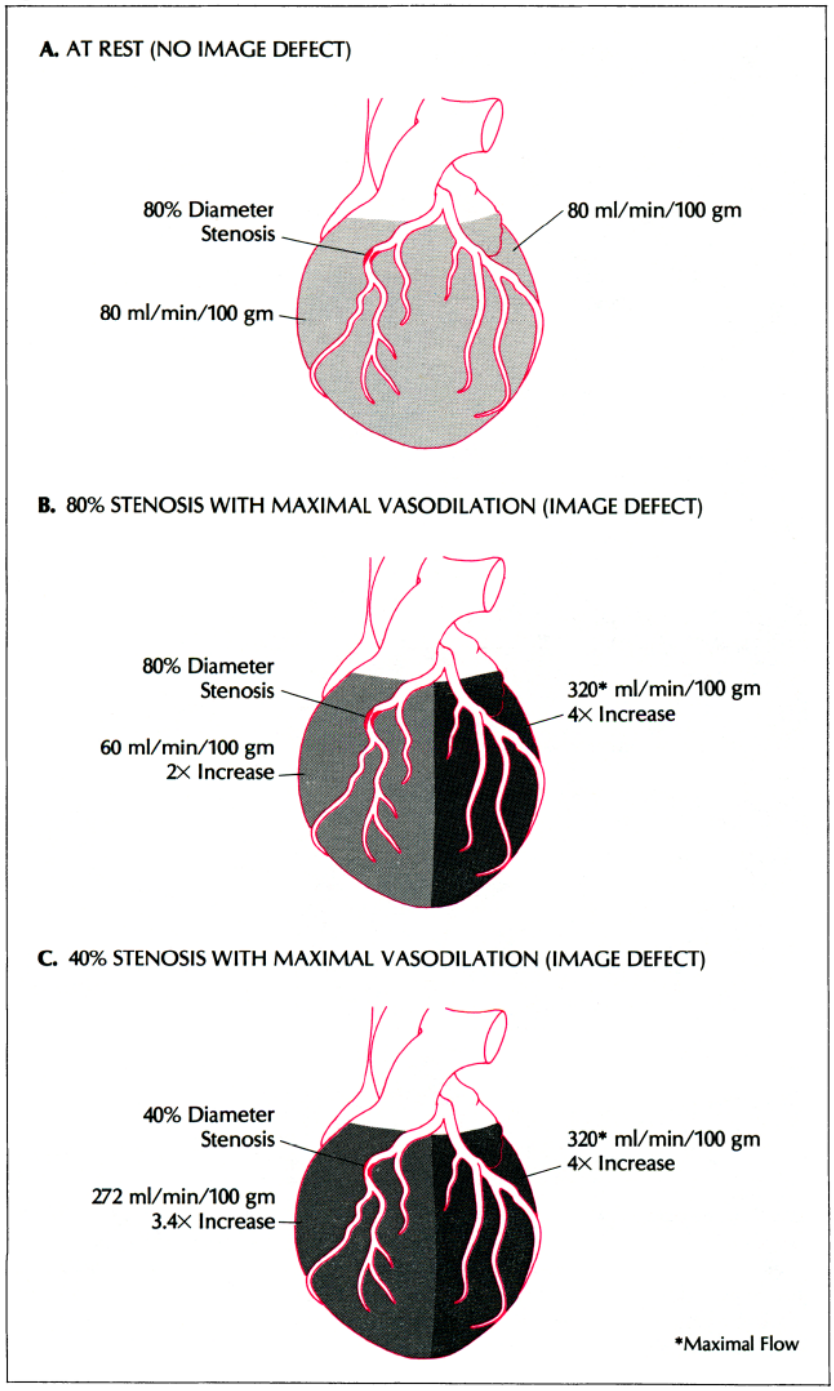
The most important element in the imaging process is subtraction, which eliminates unwanted background or extraneous densities and isolates the clinically relevant subset of signals present in the unsubtract-

Figure 3



Flow determination (F) based on extraction of tracers may be done with either labeled microspheres (left) or diffusible tracers (right). Microsphere technique requires arterial injection and tissue sampling; therefore is restricted to animal studies. Equation for determining flow does not require allowance for extraction (E) since all microspheres are trapped in capillary bed (E = 100%). Diffusible, extracted tracers may be injected intravenously and are suitable for clinical use, but extraction must be included in equation. After intravenous injection of a diffusible tracer, tissue activity, time-integrated arterial input, and first-pass extraction may be measured directly with positron camera.

Figure 4



Myocardial perfusion imaging at maximal coronary flow is a useful technique for identifying and quantifying coronary stenoses. In the presence of an 80% diameter stenosis, resting coronary blood flow is uniform in the heart, with no defect on a perfusion image (A). With vasodilation, perfusion normally increases by approximately four times, but coronary stenosis blunts this increase and defect appears in the myocardial perfusion image taken under conditions of maximal coronary vasodilation. With an 80% diameter stenosis, image defect (B) is severe, with a 50% perfusion differential between normally and abnormally perfused areas. At maximal coronary flow (C) even a 40% diameter stenosis produces a mild relative disparity in perfusion compared with a normal artery. Therefore, an accurate positron camera, which can measure small differences in perfusion in different parts of the heart, can detect mild stenosis under conditions of maximal coronary flow.

ed image. However, the technique is subject to errors caused by cardiac and respiratory motions, which create artifacts in the subtracted image and degrade spatial resolution. Although digital angiography has poorer spatial resolution than standard radiographic film techniques, it is characterized by better contrast recognition, which allows intravenous rather than intracardiac injection of contrast medium; this is the primary advantage of this technique.

Digital subtraction angiography with intravenous injection of contrast medium has been successfully used to visualize the left ventricle and accurately measure the global ejection fraction. However, motion artifacts have significantly limited its utility for exercise testing. Furthermore, the large volume of contrast medium injected intravenously causes hemodynamic alterations, particularly in left ventricular loading.

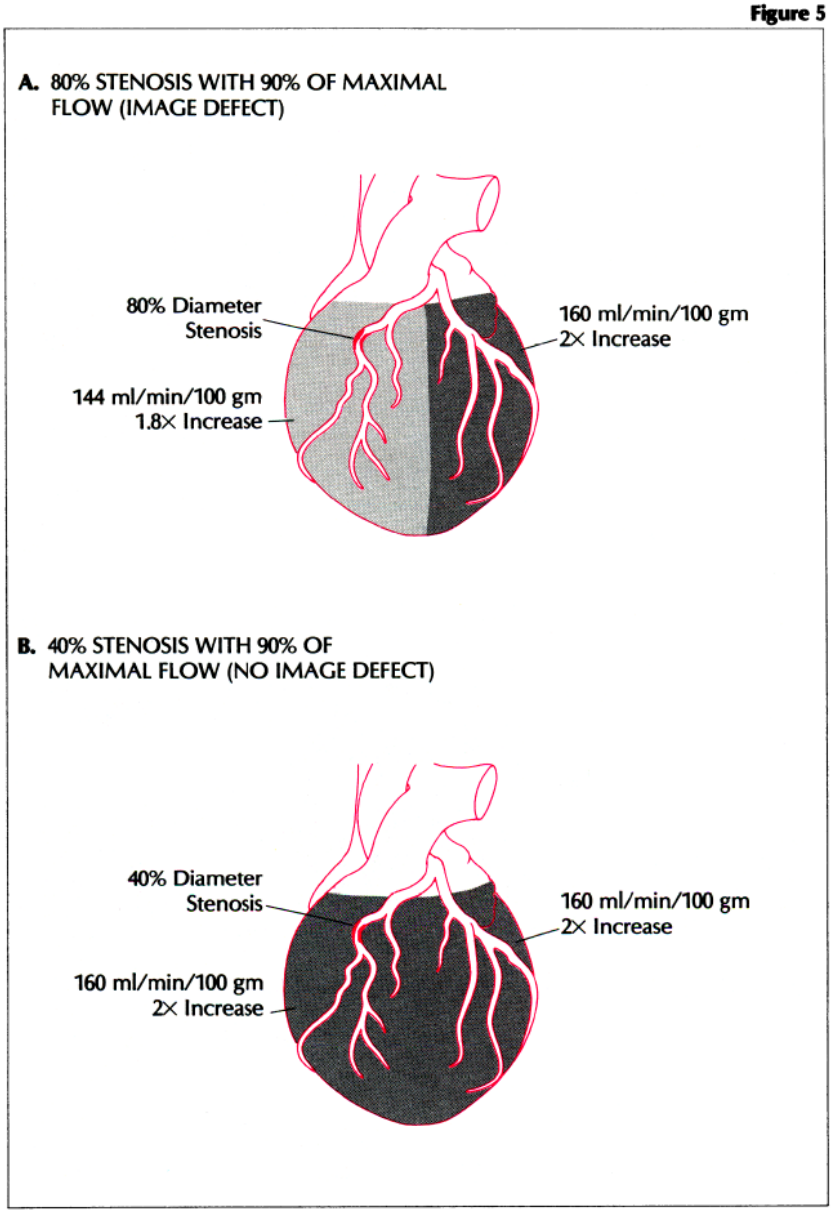
Human coronary arteries have not been adequately visualized with digital subtraction angiography after intravenous injection of contrast medium. The coronaries are more difficult to visualize than any other arteries because they are smaller, they are moving, they overlap the densely opacified left ventricle and aorta, and they are easily confused with surrounding background structures, such as residually opacified pulmonary veins. However, in the aorta and peripheral arteries, intravenous digital subtraction angiography has great potential as a substitute for standard arteriography. Thus, its potential lies primarily in its ability to produce peripheral arteriograms without invasive catheterization. Its role in functional and dynamic imag-

ing of the heart is limited primarily to resting left ventricular function.

Cardiovascular CT scanning. Fast CT scanners are currently being developed for cardiac applications. In prototype instruments, scanning speed has increased to the one-second range, spatial resolution has improved to one or two line pairs per millimeter, and density resolution also has shown considerable improvement. The mechanical motion of conventional scanners is being replaced by magnetic deflection of an electron beam against an extended tungsten target that emits x-rays as the electron beam passes across its surface. The pencil x-ray beam then fans across the patient and is picked up by a single elongated scintillation detector opposite the tungsten target. Preliminary information from cardiac CT scanning demonstrates that it may be possible to obtain tomographic images of the heart that show left ventricular function and wall thickness. However, the fundamental information provided is limited to the x-ray image of anatomic borders changing with time. Direct measurements of metabolism and blood flow are not feasible, and x-ray CT scanning probably will not facilitate early diagnosis of coronary disease or assessment of myocardial metabolic abnormalities.

Nuclear magnetic resonance. Some atomic nuclei, such as those of hydrogen and phosphorus-31, have odd numbers of protons and neutrons. These nuclei may therefore exhibit net spin, which generates small magnetic fields, causing the nuclei to behave like tiny magnets (see W. H. Oldendorf, "NMR Imaging: Its Potential Clinical Impact," HP, September 1982). When placed in a strong external magnetic field, the nuclei align along the magnetic lines of force and assume a low-energy state. A weak, rapidly alternating magnetic field (radio frequency), transmitted at the resonant frequency of the nuclei, will change the orientation of the nuclei relative to the strong magnetic field. The absorption of the radio frequency energy causes the nuclei to realign against the strong field and to increase their energy state. After cessation of the radio frequency transmission, the perturbed nuclei return to the equilibrium state, or precess

Figure 5



Perfusion imaging of maximal coronary flow for the detection of coronary stenosis does have limitations, particularly when coronary flow cannot be increased to maximal levels. Even in the presence of a severe coronary stenosis (A), relative increase in flow between normal and abnormal areas is small and may not be detected. Milder stenosis (B) cannot be detected, since there is no difference in the relative perfusion of the myocardium.

back to align with the strong magnetic field and release the absorbed radio frequency energy. The process of reorientation to the low-energy state is known as relaxation, which occurs in two modes: longitudinal (or spin-lattice) relaxation, described by the time constant T_1, and transverse (or spin-spin) relaxation, described by the time constant T_2.

Information on spatial distribution of the released radio frequency energy during relaxation can be obtained by utilizing the dependence of the resonant frequency of each nucleus on the strong magnetic field. By varying the strong field through the target volume by definite increments, it is possible to use the frequency of the return original to select or locate the source of the radio frequency energy. The strength of the signal at each frequency is proportional to the density of the nuclei in the sample plane. Good spatial resolution requires several minutes to detect the strongest signal from protons. Therefore, motion is an important problem in NMR imaging, limiting its usefulness.

The strength of the received signal for constructing NMR images depends on the abundance of the nuclei in the target as well as on their intrinsic ability to produce a strong signal. Currently, only protons are in sufficient abundance (approximately 70%) and have a sufficiently strong inherent signal for clinical NMR imaging. The parameters measurable by NMR are proton concentration and the T_1 and T_2 relaxation times. By comparison, the phosphorus signals from ATP, for example, are weaker than the proton signals from water by a factor of one million, because the concentration of phosphorus compounds is less than the concentration of hydrogen and the inherent signal is not as strong. Consequently, it will probably not be possible to obtain NMR images of phosphorus compounds in the heart with any useful spatial resolution.

The most important characteristic of NMR for clinical imaging is that there are marked differences in relaxation times in soft tissues, such as fat, muscle, and blood—out of proportion to their differences in proton concentration. Consequently, it is possible to differentiate among these types of tissue by an almost twofold difference in T_1 measurement; by comparison, x-ray attenuation coefficients differ by only a few percentage points for these tissues. Thus, NMR imaging is a powerful and useful technique for cross-sectional imaging of the brain, where white matter is high in lipid content and gray matter is high in water content.

Blood flow in cerebral vessels also has been described recently with NMR techniques used to examine other relatively nonmobile vessels of the body. However, although NMR is theoretically useful for detecting fatty deposits in arteries at an early stage of atherosclerosis, application to the coronary arteries will be extremely difficult because of their small size, motion, and the fact that they are embedded in a fatty sheath. It does not seem probable, therefore, that early diagnosis of coronary artery disease or measurements of myocardial perfusion or cardiac metabolism will be clinically feasible with NMR.

Positron emission tomography provides quantitative measurements and demonstrates distribution of metabolism and perfusion.

A positron is a positively charged electron emitted by certain unstable atoms in the process of radioactive decay, such as carbon-11, oxygen-15, nitrogen-13, and fluorine-18. This positron travels several millimeters in tissue and annihilates when it collides with a negative electron, giving off two 511-kev photons in opposite directions, as shown in Figure 1. The annihilation photon pair can be detected with a pair of radiation detectors connected through a coincidence counting circuit, so that one decay is recorded if both detectors are activated simultaneously by the photon pair. Decays that occur outside the sample volume between the detectors are excluded from the count data, since the striking of only one of the detectors by one of the photon pair is not counted. Collimation, or exclusion of stray radiation, is therefore accomplished electronically with positron detection rather than with lead collimators, as it is done in single-photon imaging. Electronic collimation is much more efficient than lead collimation, since it counts all of the activity in the sample volume between the coincident detectors.

With appropriately fast electronics, it is also possible to measure the difference in time required for the photons in a pair to reach their respective detectors, when the site of annihilation is closer to one of the detectors. By measuring this time difference, the site of annihilation can be approximately located in the sample volume between the two detectors. (The time difference between arrivals of paired photons traveling different distances at the speed of light is in the range of 300 to 400 psec [1 psec$=1\times10^{-12}$ sec].)

This time-of-flight information thereby provides a priori knowledge of the distribution of radioactivity in the sample volume even before computer reconstruction of the image. With a series of coincident detectors in a ring, a cross-sectional tomographic image may be reconstructed with techniques similar to those used for conventional x-ray CT scanning.

The primary difference between positron tomography and x-ray CT scanning is the source of radiation. In CT scanning, an external tube gives off an x-ray beam, which passes through the target to a detector that measures attenuation. In positron imaging, the source of radiation is an intravenously injected radionuclide located in the particular organ being imaged. Since the positron emitters are isotopes of carbon, oxygen, nitrogen, and fluorine, many natural organic compounds in the body can be labeled for imaging metabolic processes in intact subjects. Because the half-lives of positron radionuclides are short, repeated imaging may be carried out with minimal radiation burden to the patient. Positron imaging is therefore useful for measuring myocardial perfusion, metabolism, and function in normal or pathologic states. Figure 2 shows cardiac cross-sectional and longitudinal tomographs of intravenously injected rubidium-82, a positron-emitting perfusion tracer.

As demonstrated by N. Mullani and R. Goldstein in our laboratory, regional myocardial perfusion can be determined with a diffusible, extracted tracer, such as ^{82}Rb or ^{13}N ammonia, after intravenous bolus injection, using the formula:

$$\text{Flow} = \frac{\text{Myocardial Uptake}}{\text{Extraction} \times \text{Total Delivered Dose}}$$

Extraction is the percent of radionuclide extracted by the organ in the first pass of radiotracer through that organ, and total delivered dose is the mathematical integration of time and arterial concentration of radionuclide during the time of myocardial uptake.

Basic concepts underlying quantitative imaging. In order to interpret and apply this powerful new tool clinically, it is useful to understand the basic concepts of how metabolic or flow tracers behave in the body. The clearest way of explaining these concepts is to begin with a simple animal model and then extend that idea to the more realistic concepts applicable clinically.

For measuring blood flow with labeled microspheres in experimental animals, the formula for determining flow is used with extraction equal to one, or 100%, since the microspheres are completely trapped in the myocardial capillaries after left atrial injection. At the time of injection, an arterial reference sample is withdrawn at a known rate and volume in order to determine the dose delivered to all arterial beds. The animal is then sacrificed or the myocardium is biopsied in order to determine tissue uptake; flow is calculated. Since this technique requires left atrial injection to assure proper mixing of the tracer, as well as tissue samples to count myocardial uptake of activity, it is not suitable for patient or noninvasive studies.

In contrast, diffusible tracers are only partially extracted (extraction < 1). The percent of tracer extracted falls as flow increases. Since extraction is variable and dependent on flow, accurate flow determinations require measurement of extraction of the radiotracer in its first pass through the organ after intravenous injection. These concepts are illustrated in Figure 3.

How are these ideas related to a clinician looking at the radionuclide image of a patient's heart or other organ? The picture provided by the current imaging tools, such as the standard gamma camera, shows the distribution of tracer uptake in the organ. As described, uptake is only an indirect index of perfusion, as follows:

$$F \times E = \frac{\text{Myocardial Uptake}}{\text{Delivered Dose}}$$

Since the delivered dose is the same for the various regions of an organ for a given single injection, relative regional uptake in an organ is given by a simplified equation:

$$F \times E = \text{Relative Regional Myocardial Uptake}$$

This relative uptake of activity is linearly related to flow at normal control levels of myocardial flow. However, at high flow it underestimates true flow, since extraction decreases at high flow as a result of decreased residence time of the tracer for extraction. Low flow is overestimated, because extraction is increased as a result of long residence time.

Extraction at any given flow may also be altered independently by such factors as pH and the presence of membrane-active

drugs. Therefore, the image seen by the clinician shows the regional distribution in the organ of the net uptake of radionuclide tracer as affected by both metabolically dependent extraction into the tissue and by blood flow to that tissue.

In order to separate the metabolically dependent process of extraction from the measurement of blood flow, we have developed a method for measuring the first-pass extraction of partially extracted positron radionuclides after intravenous injection. Myocardial perfusion can then be accurately measured by determining uptake, integrated time-arterial activity, and extraction.

Clinical Diagnosis of Early CAD

Flow through a mild-to-moderately stenotic coronary artery is generally normal at rest. Exercise or a coronary vasodilator increases flow through the stenosis but only to submaximal levels, thereby producing a disparity in regional perfusion relative to areas supplied by a normal coronary artery, as shown in Figure 4. This disparity at high coronary blood flow can be imaged noninvasively, using diffusible tracers, to diagnose coronary disease. The quantitative severity of the perfusion defect is proportional to the severity of the stenosis. If marked increases in coronary flow can be induced, mild early coronary stenoses can be identified before symptoms or infarction occur; medical therapy can then be aimed at reversal of coronary atherosclerosis. However, with modest increases in coronary flow, only severe coronary stenoses can be identified (see Figure 5). An inadequate stimulus for increasing coronary flow or an inadequate perfusion imaging agent or technique will limit the ability to detect or quantify coronary stenoses.

Positron emission tomography of myocardial uptake using ^{13}N ammonia had a sensitivity of 97% and specificity of 100% for detecting significant coronary artery disease in a preliminary study with only a small group of patients. However, ^{13}N ammonia requires an on-site cyclotron, costing up to $2 million, and thus is not practical for widespread use.

^{82}Rb, a positron-emitting diffusible tracer, can be obtained from a desk-top generator system. The half-life of ^{82}Rb is 74 seconds, while that of the parent isotope in the generator, strontium-82, is 25 days. Thus, the longer-lived generator provides a short-lived daughter isotope that can be used for a month or more for imaging purposes without the need for an on-site cyclotron.

In initial studies we developed a mathematical model to determine the extraction of ^{82}Rb after an intravenous bolus. Regional flow in dogs was accurately measured with this approach at coronary flows up to seven times normal with a variety of metabolic conditions, including alkalosis, acidosis, and ischemia, and pharmacologic interventions, including administration of digoxin, catecholamines, propranolol, and glucose-insulin infusion.

Measurement of absolute and relative myocardial perfusion with the new TOFPET, designed and constructed by N. Mullani in our laboratory, is sufficiently accurate to differentiate relatively small (15%) disparities in maximal coronary flow required to identify mild coronary stenoses. By comparison, flow differences by a factor of two to three are required for observation of defects on planar thallium images.

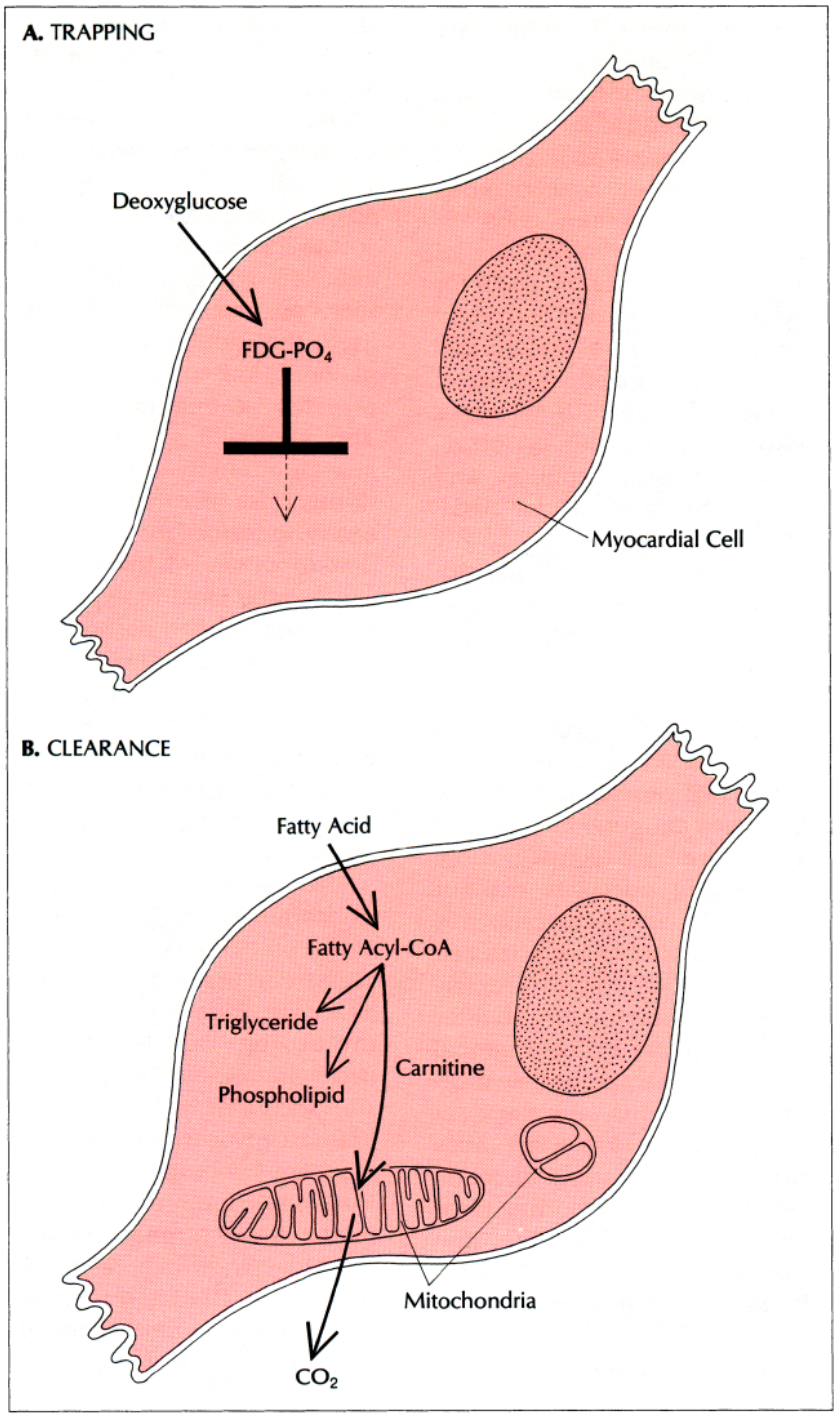
The availability of a commercial rubidium generator and development of less expensive positron cameras will make accurate measurement of myocardial flow widely available. Furthermore, since ^{82}Rb is short-lived, the radiation dose to the patient is low and studies can be repeated at frequent intervals. This approach may establish a new standard by which patients at high risk of coronary disease can be identified and followed.

Metabolism. Positron isotopes can also be used to expand our knowledge of the pathophysiology of myocardial disease. Compounds labeled with positron isotopes of carbon, oxygen, nitrogen, or fluorine can be used to determine the rate of uptake and metabolism of specific substrates in metabolic pathways.

The assessment of substrate utilization generally involves one of two processes: metabolic trapping in an organ and metabolic clearance from the organ (Figure 6). For example, 2-fluoro-2-deoxyglucose labeled with fluorine-18 (FDG) has been used to evaluate myocardial glucose metabolism. Like unlabeled glucose, FDG is taken up into cells. Within the cell it is phosphorylated to FDG-PO_4, which is not further metabolized and is trapped in the cell. (It is neither metabolized nor broken down because there is no glucose-6-phosphatase in the heart.) Therefore, the amount of FDG taken up by myocardium is proportional to the rate of glucose uptake and is a measure of the level of glucose metabolism.

Preliminary studies at UCLA by H. R. Schelbert and asso-

Figure 6



Assessment of substrate utilization generally involves one of two metabolic mechanisms: trapping in an organ (A) or clearance from the organ (B). Trapping is exemplified by ^{18}F-labeled deoxyglucose (FDG), which is transported across myocardial cell membrane and phosphorylated. However, the fluorinated deoxyglucose-phosphate complex does not proceed down the metabolic chain and is metabolically trapped within the cell. Therefore, the rate of accumulation of FDG in the myocardium reflects the rate of glucose uptake and is an indirect measure of glucose metabolism. On the other hand, fatty acids (B) are trapped to some extent in tissue but their metabolite CO_2 is cleared. Labeling the fatty acids will result in clearance of labeled CO_2, which can be measured to evaluate the rate of myocardial fatty acid metabolism.

ciates demonstrated that in injured but viable ischemic myocardium, fatty acid metabolism may be markedly depressed while glucose uptake is increased, suggesting increased anaerobic metabolism of glucose. With further injury causing cellular necrosis, the uptake of glucose is suppressed. These observations thus indicate whether ischemic myocardium is injured but viable or irreversibly damaged. The same group has also demonstrated increased glucose uptake in the inferior posterior myocardium of patients with Duchenne-type muscular dystrophy who develop cardiomyopathy.

As demonstrated by Goldstein, the metabolic clearance of ^{11}C palmitic acid can be used to determine the rate of fatty acid oxidation, which is the major source of energy for the heart. ^{11}C palmitate is effectively trapped after intracellular activation. The only mode of egress is via oxidation in the mitochondria yielding ATP and $^{11}CO_2$ (which diffuses out of the cell). Therefore, the rate of decrease in ^{11}C radioactivity is proportional to the rate of oxidation. An appropriate transport model of palmitate kinetics would provide measurements of metabolic rates in humans equivalent to those previously obtainable only in isolated hearts or after biopsies in in vivo studies.

Cardiomyopathies. The balance between fatty acid, carbohydrate, and amino acid metabolism may be crucial in the development of clinical disease. For example, diabetic hearts rely on fatty acids almost exclusively, whereas glucose oxidation is minimal. The ability to assess the metabolic state of the heart in these patients may lead to a better understanding of the

mechanism of diminished contractility and may also facilitate earlier detection of the cardiomyopathic process and provide a guide to therapy. In patients with volume or pressure overload, the factors responsible for progressive decreases in contractility have not yet been identified. Amino acid incorporation into protein in hypertrophied hearts may prove to be an important phenomenon for study by positron tomography, since the degree of hypertrophy may be related to the heart's ability to compensate for abnormally high work loads. On the other hand, hypertrophy may also relate to diffuse fibrosis caused by myofibrillar enlargement to such an extent that diffusion of oxygen is impaired and function deteriorates. This process can be examined directly by positron imaging.

Myocardial infarction. One of the major research areas of the past decade involves salvage of myocardium during acute myocardial infarction. Since most of the experiments were done in animals, infarct size was measured by histology. However, since the animals did not have preexisting coronary disease, extrapolation of the results to humans is difficult.

The tests used to estimate infarct size in humans include creatine kinase release, technetium-99m pyrophosphate uptake, precordial ST-segment mapping, and thallium scintigraphy. These techniques have been of limited clinical value in answering the necessary questions and, more important, cannot differentiate potentially salvageable myocardium from irreversibly injured tissue. The ability to define spatial extent—as well as metabolic degree of myocardial injury—is of profound clinical importance in view of the availability and benefits of coronary thrombolysis and other pharmacologic interventions during acute infarction.

In addition to FDG, ^{11}C pyruvate has great potential for use in studying myocardial infarction. Goldstein demonstrated that labeled pyruvate is metabolized rapidly and cleared by normal tissue but is converted to lactate by ischemic tissue, where it persists in the ischemic region. After intravenous injection of labeled pyruvate, viable ischemic myocardium can be identified by its increased accumulation of labeled lactate.

Positron imaging, therefore, provides quantitative information about perfusion and metabolism, with the potential for early detection of coronary disease and identification of ischemic, reversibly damaged, viable myocardium. It also may provide insights into the metabolic mechanisms underlying cardiomyopathies. The potential availability of generator-produced positron isotopes (^{82}Rb) and simpler, cheaper positron cameras may make positron imaging widely available for the measurement of regional blood flow—a possibility with profoundly important diagnostic and therapeutic implications. □

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ANNOUNCEMENTS

Wellcome Visiting Professorships in Basic Medical Sciences, 1984–85

The Burroughs Wellcome Fund is sponsoring the eighth series of Wellcome Visiting Professorships in the Basic Medical Sciences for the academic year 1984–85. These awards will be administered by the Federation of American Societies for Experimental Biology. Visiting professorships are intended to stimulate interest in basic sciences and enhance communication with scientists in Biological Chemistry, Immunology, Nutrition, Pathology, Pharmacology, Physiology, and Cell Biology. Twenty-one awards will be made, three in each discipline. Each professorship carries a $1,500 honorarium plus travel expenses. The Burroughs Wellcome Fund also provides $250 to each host institution. Institutions chosen to receive Wellcome Visiting Professors in the Basic Medical Sciences will engage distinguished researchers from the United States or abroad who will spend 2–5 days at the institution in teaching and discussion with students and faculty. The Visiting Professor will also deliver a Wellcome Lecture on a subject related to the specific discipline.
Deadline: May 1, 1984. *Information:* Dr. R. W. Krauss, Executive Director, The Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, MD 20814.

Midwest Neurobiology Meeting

The Midwest Neurobiology Annual Meeting will be held April 6–8, 1984, at Washington University, St. Louis, MO. The program will include submitted posters and talks, laboratory demonstrations, an address by Tom Carew on "Learning and Memory in *Aplysia,*" and a symposium on neuronal development and plasticity. *Registration deadline:* March 2, 1984. *Information:* Carl Rovainen, Dept. of Physiology and Biophysics (314/362-2299) or Paul Stein (314/889-6824), Dept. of Biology, Washington University School of Medicine, St. Louis, Mo. 63110.

NRC Resident Fellowships

With the support of the Andrew W. Mellon Foundation, the National Research Council offers a limited number of resident fellowship appointments for work with NRC or Institute of Medicine committees on issues of science and technology and national policy. The requirements of the fellowship are flexible and can be adapted to the specific needs of the Fellow and the committee of the NRC with which he or she will be working. A fellow will be expected to develop a close working relationship with a committee and to create a tangible product—one or more personally authored scholarly papers or a report to which the Fellow has made significant contributions. A committee chair or member or a senior NRC staff member will serve as mentor to the Fellow to ensure that he or she has entree to science policy communities in Washington, DC, to relevant experts across the country, and to the range of resources available within the NRC. *Information:* NRC Fellows Program JH853, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418.

FASEB 1984 Summer Conferences Series

This summer the Federation of American Societies for Experimental Biology will hold its Third Annual Summer Research Conference Series. For detailed information see the February issue of *Federation Proceedings. Topics and Chairmen:* Neural Mechanisms in Cardiovascular Regulation (June 10–15), L. Schramm, Johns Hopkins University School of Medicine; Micronutrients: Vitamin A and the Retinoids (June 17–22), F. Chytil, Vanderbilt University; Diagnosis, Toxicity and Therapy of Trichothecene Intoxication (June 24–29), R. W. Wannemacher, US Army Medical Research Institute of Infectious Diseases; Immunopharmacology (July 1–6), L. Lictenstein, Johns Hopkins University School of Medicine; Somatic Cell Genetics (July 8–13), L. Chasin, Columbia University; Receptors (July 15–20), R. Lefkowitz, Duke University Medical Center; Calcium and Cell Function (July 22–27), C. B. Klee, National Institutes of Health (NCI); Development and Aging of the Immune Function (July 29–August 3), M. E. Weksler, Cornell University Medical College; Mononuclear Cell and Antibody Networks (August 5–10), C. Janeway, Yale University Medical School; Neuronal Cell Cultures (August 12–17), P. G. Nelson, National Institutes of Health (NICHHD).

THE PHYSIOLOGY TEACHER

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Neurochemistry of Thermoregulation

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Thermoregulation is considered to be an integrated and coordinated mobilization of physiological processes used to actively defend the set temperature of the body against a cold or warm challenge both from within and without. The neurochemistry of thermoregulation had its fascinating origin at the turn of the century when Barbour found that epinephrine infused into the cerebral ventricle of the rabbit produced a transient but intense hypothermia (10). Throughout succeeding decades, other interesting observations revealed that many chemical substances could readily perturb body temperature. For example, in the 1930's it was found that excess Ca^{2+} injected directly into the hypothalamus not only evoked a fall in body temperature but blocked a febrile response due to bacterial pyrogen. Although the periods before and after World War II were largely characterized by a research void in studies of body temperature regulation, the chemical-molecular basis for an understanding of thermoregulation was unquestionably on the horizon.

Following experiments in which the intracerebroventricular (ICV) infusion of serotonin (5-HT) or a catecholamine such as norepinephrine (NE) exerted an opposite effect on the body temperature of the cat, a theory was proposed that a balance in the release of monoamines in the hypothalamus constituted the synaptic mechanism by which thermoregulation was achieved (5). In the two decades since the monoamine theory was initially put forth, a number of important physiological precepts and modifications have emerged.

First, distinct regions of the diencephalon are neurochemically unique in that different nerve cells contain different neuroactive substances. Anatomically, many regions exhibit a sensitivity to a physical stimulus: the anterior hypothalamic-preoptic area (AH/POA) contains subpopulations of neurons that are distinctively thermosensitive. That is, certain neurons alter their firing rate in response to cold, other cells in response to heat, and still others when the local temperature deviates in either direction (2). In this context, cells of the AH/POA are specifically reactive to biogenic amines, pyrogens, anesthetics, and other substances in relation to a thermoregulatory response. Still other regions of the hypothalamus are both chemically and thermally "blind" (11).

Second, a chemical substance administered peripherally or centrally does not necessarily play a functional role in the hypothalamic mechanism for thermoregulation simply because the animal's core temperature rises or falls. A change in body temperature often is secondary to a generalized impairment of the animal's physiological status (10). Under a condition of functional incapacitation, body temperature would decline when the ambient temperature is below the level of metabolic equilibrium and thermoneutrality. Whether the temperature response to the pharmacological compound is due to peripheral effects, e.g., vasomotor tone, metabolism, or respiratory rate, is always a critical issue for one's interpretation (12).

Third, the diverse control mechanisms involved in thermoregulation in most mammalian species studied thus far are located principally in the hypothalamus. Lesion studies in the 1930's involving this structure bolstered the clinical belief that the AH/POA comprised the "heat-loss center," whereas the posterior hypothalamus (PH) represented the "heat-gain center." For over 10 years we have known that this idea is incorrect. Unfortunately, most textbooks of physiology used for teaching students at all levels perpetuated this mistaken concept until very recently.

Thus, among the questions that still concern thermoregulatory physiology today are the following. Is a hyperthermia equivalent to a fever? How is the core temperature established by the hypothalamus at 37°C, i.e., the so-called set-point temperature? Which neuronal mechanisms in the hypothalamus defend this set point and thus regulate core temperature? What neuronal mechanism in this structure shifts the set-point temperature during the fever of bacterial origin? Does an antipyretic drug functionally reverse the latter mechanism? In this survey, experimental findings that offer partial explanations of these difficult issues will be presented.

Aminergic Synapses and Thermoregulation

Quite remarkably, the neurochemical events relating to thermoregulation coalesce anatomically with the classical findings based on tissue ablation and electrophysiological recording. This anatomical concordance is a crucial point.[1] In this context, a succession of related experimental observations have blended together to produce a coherent explanation of thermoregulatory events at the synaptic level.

Thermoregulatory equilibrium is achieved by the following mechanisms within the thermosensitive region of the AH/POA (2). Cold-sensitive neurons are thought to integrate sensory input and then trigger the effector pathways for metabolic heat production, vasoconstriction, shivering, and other responses. On the other hand, to activate heat loss warm-sensitive neurons stimulate effector pathways for vasodilation, panting, perspiration, reduction in metabolic rate, and inhibition of the effectors for heat production. Although the temperature of the blood circulating within the hypothalamus participates in the feedback control of this sensor-effector system, receptors in the skin provide critical thermal signals transmitted via afferent fibers to the AH/POA. Cells in the PH are essentially insensitive to a deflection in their own local temperature.

Although the monoamine theory of thermoregulation was based initially on experiments utilizing the ICV approach (5), it was later found that 5-HT injected into the AH/POA of the monkey produces a rise in body temperature accompanied by piloerection, shivering, and vasoconstriction (10). Conversely, NE microinjected at the same site evokes a hypothermia, vasodilation, and responses that are a "mirror image" of the action of 5-HT. Not only are these opposing functional responses dose dependent, but pharmacological antagonists of indole and catecholamine receptors block them, respectively. An often-overlooked facet of the action of monoamines on AH/POA is the insensitivity of cells of the PH to the amines.

From this set of pharmacological observations are the results of a large series of experiments summarized in Table 1. A pivotal finding is the demonstration that exposure of the animal to a cold ambient temperature enhances the release of 5-HT from AH/POA, where exposure to heat liberates catecholamines from the same anatomical site (12). In addition, destruction of 5-HT or catecholamine-containing neurons in the AH/POA by two relatively selective neurotoxins incapacitates respectively the normal thermoregulatory responses to a cold or warm challenge (Table 1).

One issue raised in the 1960's by the monoamine theory dwelt on the cellular effects of the synaptic information provided by the monoaminergic neurons in the AH/POA. Would impulses from aminergic neurons be translated along an effector system? And by what anatomical route would each travel? In the late 1960's, endogenous acetylcholine (ACh) was implicated through its presynaptic release in efferent pathways that traverse the hypothalamus and mesencephalon (11). Experimental results on the linking nature of cholinergic neurons showed that *1*) ACh evokes a rapid, short-lived and differential hyper- or hypothermic response when applied locally to the hypothalamus; *2*) the release of ACh in mid- and caudal regions of the hypothalamus occurs in response to the application of monoamines to the AH/POA; *3*) ACh release is enhanced at sites within the hypothalamus after exposure of the animal to cold air to a far greater extent than to warm air; and *4*) thermogenic responses, including those produced by a cholinomimetic or a bacterial pyrogen, are antagonized by a muscarinic receptor blocker.

Table 1
Summary Observations Related to Role of Endogenous 5-HT and Catecholamines in the Anterior Hypothalamic-Preoptic Area Mechanism for Thermoregulation in Primate or Cat

I. Indirect Evidence

A. Intraventricular injection of serotonin (5-HT) and catecholamines (CA) evokes hyper- and hypothermia, respectively

B. Specific receptor blocking agents for 5-HT and CA antagonize the respective temperature changes

II. Anatomical Evidence

A. Nerve terminals containing 5-HT and CA are present in anterior hypothalamic-preoptic area (AH/POA) which contains temperature sensitive neurons

B. Dose-dependent hyper- and hypothermia are produced by 5-HT and CA, respectively, when microinjected into AH/POA.

C. Blockade of temperature responses is produced by local application to AH/POA of respective antagonist of 5-HT or CA receptors

D. Peripheral cooling or heating of animal evokes presynaptic release of endogenous 5-HT or CA, respectively, from AH/POA

E. Localized lesioning of AH/POA by a nerve terminal neurotoxin, 5, 6-dihydroxytryptamine or 6-hydroxydopamine, impairs body's defense against exposure to cold or warm ambient temperature, respectively

F. Application of 5-HT or CA to the AH/POA causes differential release of acetylcholine in mid- and caudal hypothalamus. Amines simultaneously cause selective perturbation of Ca^{2+} efflux from posterior hypothalamic area as temperature change ensues.

From Ref. 11.

Although well over 1,000 papers have been published worldwide on every conceivable aspect of this composite aminergic theory (3), disagreements nevertheless persist on the precise way in which each of these endogenous substances operate. Inconsistency in observation can be explained often on the basis of the dose of amine used, the route and time of its administration, or other technical matter. Insofar as postulated differences between species exist, even now this puzzle cannot be ignored; however, the ambient temperature of the test animal during an experiment apparently is substantially more critical than previously recognized. For example, when the rabbit is kept at a laboratory temperature of 22°C, it may respond very differently to an intrahypothalamic monoamine than if maintained at an environmental temperature of approximately 15°C, which approaches its thermoneutral zone (14).

Finally, if a discrepancy that would lead to a rejection of a part or all of the amine theory is based on the results with pharmacological agonists, an alternative experimental strategy is required. That is, the resolution to a functional question of a transmitter action always is the demonstration of its functionally evoked release

[1] Should a postulated neurotransmitter for thermoregulation exert its action only on the septum pellucidum but not on thermosensitive cells in AH/POA, a functional interpretation would be difficult to envisage.

(11). In the case of the monoamines or ACh, when such an experiment is undertaken, a differential and specific release of each substance in response to a warm or cold challenge has been consistent (Table 1). In relation to this, however, the neurochemical findings summarized in Table 1 do not always correspond with electrophysiological studies employing the iontophoresis of an amine on a single nerve cell in AH/POA. Although data obtained with this approach are both for and against the aminergic theory, the method may not be technically appropriate at the receptor level for the precise elucidation of the synaptic role played by a given neurohumoral factor (10).

Ionic Mechanism for Temperature Set Point

Extensive evidence favors the existence of a number of physiological references or "set points" around which bodily processes are continually adjusted and regulated. The set point for body temperature is considered by some physiologists to be inherently established as a built-in reference temperature at about 37 °C in many mammals, around which regulatory adjustments are made. Thus this metabolically efficient body temperature is defended and sustained (13).

From a functional standpoint, the set-point mechanism in the brain would have to be anatomically separated from the regulatory process. That is, a neuron which is responsible for holding one's set temperature would be independent of the neuron which senses a temperature change and then initiates a regulatory response. Actually, when the set-point temperature is elevated during a fever, a neuronal mechanism in the AH/POA defends the newly elevated temperature by regulatory processes in response to a cold or warm challenge.

In the early 1970's, the proposal was put forth that the ratio of Na^+ to Ca^{2+} within the PH is the fundamental process which establishes the temperature set point (13). The pharmacological and physiological evidence related to the ionic theory are presented in Table 2.

Essentially, when the ionic milieu of the PH, not the AH/POA, is perturbed by perfusion of either excess Na^+ or Ca^{2+}, the body temperature of the animal undergoes an immediate and sustained change that persists as long as the imbalance in ions is maintained. As shown in Table 2, the ratio of Na^+ to Ca^{2+} is functionally and anatomically specific. The functional effect of the ions is universal across species. In addition, if the set-point temperature is reset to a new high or low level by continual perfusion of either cation, the animal defends this new set temperature in response to a hot or cold ambient temperature.

Other experimental tests of the ionic theory showed that the efflux of endogenous membrane cations is altered in relation to body temperature. With radiotracer methods, it has been demonstrated in the cat that a bacterial pyrogen evokes a reciprocal efflux of Na^+ and Ca^{2+} ions as the fever develops. An antipyretic reverses the respective kinetics of efflux of the two cations. Moreover, the flux of Ca^{2+} is specifically shifted by *1)* local warming or heating of the AH/POA; *2)* neurotransmitters that evoke a rise or fall in core temperature; and *3)* by a severe challenge, hot or cold, of the animal's environmental temperature. Even an anesthetic drug that impairs both regulatory and set-point mechanisms, when applied directly to the AH/POA (Table 2), **IIF**), exerts an equally powerful impact on the kinetics of Ca^{2+} flux within the PH.

Table 2
Summary Observations on the Monkey and Cat Pertaining to Ionic Mechanisms for Temperature "Set Point" in Posterior Hypothalamus

I. Pharmacological Evidence

A. Excess Na^+ or Ca^{2+}, perfused within posterior but not other areas of hypothalamus, evokes hyper- or hypothermia, respectively

B. Set-point temperature can be reset to a level higher or lower than normal, for indefinite periods by perfusion of posterior hypothalamus (PH) with excess Na^+ or Ca^{2+}. Monkey thermoregulates normally in defense of new (ion reset) set-point

C. Na^+ and Ca^{2+} act specifically on PH in terms of nonactivity of other cations including K^+, Mg^{2+}, or Cl^-.

D. Tachyphylaxis to prolonged imbalance in Ca^{2+} or Na^+ does not occur with shift in set point. Temperature able to be driven up or down to the point of death

E. Autonomic responses, including feeding, arousal, and electroencephalogram, are relatively unaffected by imbalance in Na^+/Ca^{2+} within PH as shift in core temperature occurs

II. Physiological Evidence

A. Bacteria given by systemic route cause a reciprocal efflux of diencephalic Na^+ and Ca^{2+} as fever develops

B. During fever, a systemically administered anti-pyretic drug reverses the diencephalic efflux of Ca^{2+} as body temperature declines toward the afebrile level

C. Bacteria infused into AH/POA evoke efflux of Ca^{2+} from PH as temperature rises to fever level

D. When set-point temperature of monkey rises during vigorous exercise, Ca^{2+} efflux from diencephalon is enhanced. Alternatively, excess Ca^{2+} applied to PH attenuates exercise-induced hyperthermia

E. A severe challenge to set point by exposure to a hot or cold ambient temperature causes a fall or rise, respectively, in the efflux of Ca^{2+} within PH. Similarly, local heating or cooling of the AH/POA induces the same compensatory shift in Ca^{2+} efflux in PH

F. Anesthetic drug or other substance known to affect set-point temperature alters kinetics of Ca^{2+} efflux in PH

[From Ref. 11.]

One of the physiological applications of the ionic set-point theory is to the pathogenesis of fever, as described in the following section and portrayed schematically in Figure 1.

Neuroactive Factors and Fever

The pathogenesis of fever continues to be a most intriguing biomedical issue today. It is now certain that a febrile episode involves a functional interplay of both peripheral and central biochemical processes. However, the distinction between fever and hyperthermia is often blurred, even though both altered states of body temperature are not equivalent physiologically for several reasons, e.g., aspirin-like drugs are efficacious only during fever (16). Currently, great concern centers clinically on whether a febrile reaction to a bacterium or other pathogen does, in fact, reflect a healthy response. Recent reports in the nonprimate literature reveal that the early administration of an antipyretic drug during a fever can lead to an increase in morbidity (6).

Table 3 summarizes major steps in the periphery and central nervous system that are thought to be required for the development and maintenance of a fever. As

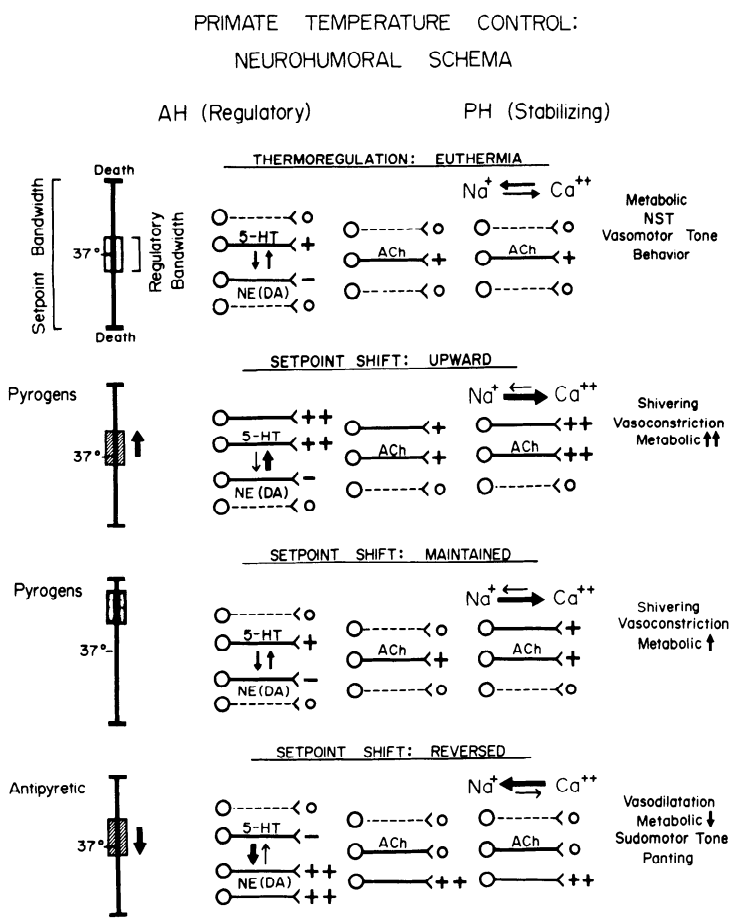


Figure 1
Neurohumoral schema depicting cellular mechanisms underlying control of body temperature in the primate. Regulatory bandwidth around optimal 37 °C set-point level is much more narrow than set-point bandwidth that can be displaced upward or downward within physiological limits of survival. As described in the text, signals from monoaminergic neurons in anterior hypothalamus (AH; regulatory) impinge upon cells in posterior hypothalamus (PH) whose ionic milieu ordinarily is intrinsically stable. Acetylcholine (ACh) transmits these signals between AH and PH. As an illustration, a pyrogen or treatment with an antipyretic drug during a fever will bring about an upward or downward shift in the set point by virtue of a coordinated set of cellular responses involving monoamines, ACh, Na^+, and Ca^{2+} ions within distinct hypothalamic regions. As a result the physiological responses (depicted on *right*) are activated. 5-HT, serotonin; NE, norepinephrine; DA, dopamine. [From Ref. 13.]

reviewed by Dinarello (4), endogenous pyrogen, a low-molecular-weight protein released from phagocytic leukocytes, is produced by the host in response to stimulation by pathogens. Although the mechanism involved in its formation is not understood, endogenous pyrogen is synthesized following transcription of new DNA and translation of messenger RNA into new protein. Interestingly, the endogenous pyrogen molecule is not species specific, and a human endogenous pyrogen can produce comparable elevations in the temperature of the monkey, rabbit, and other species. Once synthesized, the circulating pyrogenic factor reaches the hypothalamus, where it acts to induce fever. Nearly 20 years ago, the site of action of pyrogen was discovered to be the AH/POA, the neurochemical significance of which is the anatomical colocation of the action of neurotransmitters (13).

As illustrated in Table 3, endogenous pyrogen within AH/POA serves to increase the metabolism and release of 5-HT and probably to inhibit simultaneously catecholamine activity. Thus the physiological responses required for heat production are mobilized. A protein intermediary within this rostral hypothalamic area is now suspected. When new protein synthesis is reversibly inhibited by a drug such as anisomycin given directly into the AH/POA, a pyrogen fever is delayed or attenuated (15). Cholinergic neurons comprising the pathway for heat production are believed to signal the PH to shift the ionic mechanism for the set point (see above). As a result of the unbinding of Ca^{2+} ions and the consequent destablization of neuronal membranes in PH, all physiological responses including shivering, increased metabolism, and vasoconstriction are recruited for mobilization of heat production during the febrile response (13).

A schematic model of the neuronal pathways in the hypothalamus involved in the control of the body temperature of the primate as well as the responses to a pyrogen and antipyretic is presented in Fig. 1. In this composite model, the concept is portrayed of a set point with a broad bandwidth that can be shifted to a high or low temperature, hyperpyrexia, or deep hypothermia only within functional limits beyond which death occurs. The optimum set point temperature for most primates is 37 °C, at which the release of 5-HT and catecholamines is balanced in the AH/POA. Simultaneously, a steady-state equilibrium of the ionic ratio exists within the PH. Impulses from the AH/POA to the PH are transmitted by ACh, which signals sensory information pertaining to the state of thermoneutrality. In this condition, no activation of physiological responses for heat gain or heat loss is required.

In response to a pyrogen, 5-HT pathways are stimulated and the set point is shifted upward as the ionic ratio favors the cellular retention of Na^+ and extrusion of Ca^{2+} ions within the parenchyma of the PH. Figure 1 illustrates the concomitant physiological responses that accompany the upward deflection in the temperature set point. By the sustained disequilibrium in the ionic mechanism, an elevated regulated temperature is ensured. An antipyretic acts to cause a functional reversal of each of these processes. Although no evidence for crossed inhibitory pathways within AH/POA or PH exists, a reciprocal inhibition of serotonergic,

catecholaminergic, and cholinergic neurons is nevertheless presumed so that an integrated regulatory response can ensue (13).

Prostaglandins

In the 1970's prostaglandins of the E series (PGE) were postulated to participate in the genesis of fever as well as in the antipyretic action of aspirin. In spite of striking experiments on the potency of PGE in raising temperature and the efflux of PGE into the cerebrospinal fluid of an animal during fever, recent experiments do not favor PGE in the hypothalamus as being a requisite intermediary for fever (11, p. 162). In fact, "the jury is still out" on what specific role prostaglandins could play as a factor in the neuronal mechanisms underlying a febrile response.

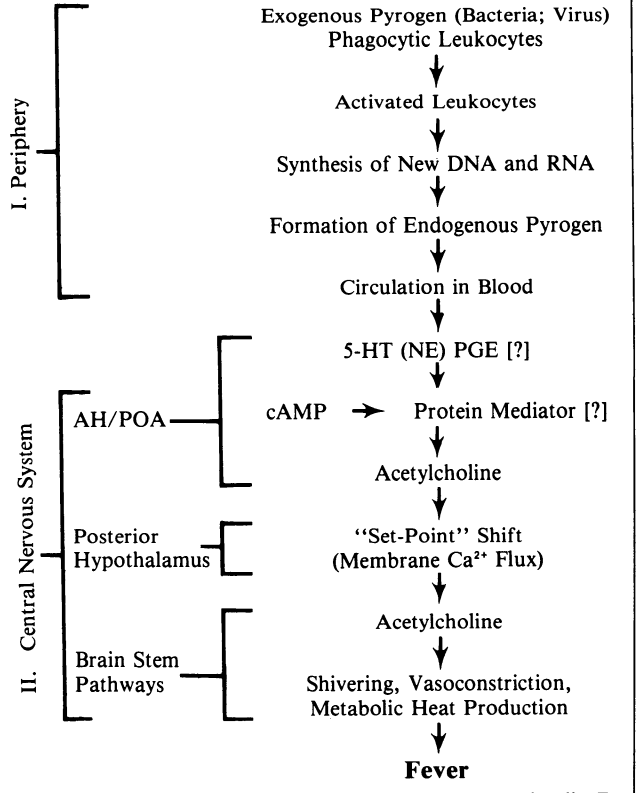
Emergence of Peptides

Within the last few years, a new class of "neuromodulator" has made its debut in the field of thermoregulation. Of several dozen endogenous peptides that could eventually be implicated in the control mechanisms for body temperature, three of the more likely candidates are adrenocorticotropin (ACTH), α-melanocyte-stimulating hormone (α-MSH), and arginine vasopressin (AVP) (9). The promise of these pituitary factors lies in the findings that they can alter core temperature when given centrally and that they are in hypothalamic tissue; immunoreactive α-MSH and ACTH are both detectable in nerve fibers in the AH/POA.

Certain peptides including thyroid-releasing hormone (TRH), bombesin, and neurotensin can induce a sharp decline in core temperature of a test animal kept at a laboratory temperature of 22°C. The physiological significance of their thermolytic action is uncertain because the hypothermic response typically is exacerbated by a cold ambient temperature and prevented by a warm temperature. In fact, neurotensin and bombesin are most likely poikilothermic agents, since they act similarly to an anesthetic drug, when administered ICV, in incapacitating thermoregulatory function and apparently the set point mechanism as well (8). Poikilothermia, a concept applied to lower vertebrate and invertebrate species, is used here, since the animal's body temperature will fall or rise as it follows the ambient temperature after injection of the peptide.

At this stage, comprehensive experimental demontrations parallel to those done for the amines are essential. The pharmacological blockade of their specific effect and a demonstration of functionally induced release from nerve cells during a temperature challenge are temporary technical obstacles which future endeavors will surmount. That scientific caution should be exercised in considering temperature changes produced by a centrally administered peptide is self-evident. Theoretically, it is possible that a peptide could serve as an "endogenous antipyretic" (6), particularly if the compound exerts a thermolytic action only when the animal is in a febrile condition (9). An equally intriguing question is how a given peptide interacts with 5-HT, NE, ACh, and/or cations implicated in the temperature sensor-effector pathways within the hypothalamus.

Table 3
Diagrammatic Steps in Development of Fever



[5-HT, Serotonin; NE, norepinephrine; PGE, prostaglandin E; AH/POA, anterior hypothalamic-preoptic area; cAMP, adenosine 3′,5′-cyclic monophosphate.]

Conclusion

The probability that transmitter substances mediate certain pivotal events in the ultimate control mechanisms for body temperature, at least for primate species, is now clear. In the final analysis, humoral mechanisms in the central nervous system underlying fever, heatstroke, vasomotor and metabolic events, cold-induced deep hypothermia, and other clinical entities surrounding thermoregulatory pathology are of both academic and medical importance. When the clinician faces the patient with a condition that pathologically disrupts the control system for body temperature, insight into the alternative mechanisms would seem essential for the adoption of a specific strategy for treatment.

To illustrate, if a victim of an automobile crash develops an intense "fever" of sudden onset, the mechanism of the febrile response may be explained provisionally by an action of 5-HT. In the primate, 5-HT infused ICV evokes an intense and rapid rise in body temperature. Since a major source of 5-HT is blood platelets, a cerebral vascular accident involving hemorrhaging into the ventricular cavity is immediately suspected. The reason is that the presence of blood in the cerebroventricular space of the primate can result in a raging hyperthermia.

A second illustration centers on the usage and contraindications of antipyretic drugs. If a fever is truly a protective physiological mechanism that represents a healthy response to an endotoxin challenge and in turn serves to inactivate bacterial and other organisms, antipyretic therapy could prolong and exacerbate the illness (7). On the other hand, antipyretics should be prescribed for the patient who is susceptible to febrile con-

vulsions or develops an unusual hyperpyrexia, is in an early stage of pregnancy, or possesses a cardiovascular disorder. Overall a decision on a therapeutic regimen of an antipyretic can be made rationally if fundamental physiological mechanisms are understood (6).

Conflicting Viewpoint

Historically, certain results of temperature experiments done in nonprimate species (1) do not always agree with the neurochemical model of thermoregulation developed for the primate. How is a discrepancy in observation which may lead to an alternative model resolved?

First, the present neurochemical concepts of thermoregulation are based on a coherent set of consistent physiological findings with the monkey (and/or cat) (Table 1). Each of these meshes independently with the pharmacological finding that amines in AH/POA function in the thermoregulatory mechanism. Thus, if an isolated experiment with one species is in disagreement, the result is considered in light of the particular experimental method employed.

Second, in the case of a putative neurotransmitter such as a catecholamine, the main question is whether a thermal stimulus enhances or suppresses its presynaptic release from the AH/POA. If so, does a warm or cold ambient temperature determine the characteristics of the amine's release? The importance of this criterion of the release of amine or other factor cannot be overemphasized, because one assumes that the action of a pharmacological agonist mimics or simulates what actually transpires at the synapse. But because of the multiplicity of local effects exerted by any neuroactive substance on membranes, blood vessels, Na^+ or Ca^{2+} transport, local metabolism, and so forth, this presumed simulation may not be true.

Future Prospect

On the frontier of research in the field of thermoregulation is the exciting prospect that the details of the neurochemistry of this vital function will be comprehended more completely. For example, the physiological relationship between the anterior and posterior hypothalamus, in terms of feedback systems, is not yet clear. Equally significant will be the future elucidation of the unique neurohumoral processes underlying both the entry into and the arousal from the state of hibernation as well as the controlled induction of hypothermia. In each case, it is envisaged that a thorough understanding of the special mechanisms for the control of body temperature will ultimately have direct and beneficial applications to clinical medicine.

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Blood-Circulated Sciatic Nerve-Gastrocnemius Muscle Preparation in the Spinal Toad

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The isolated sciatic nerve-gastrocnemius muscle preparation from the frog or toad has a long history (3) and is still widely used in the teaching of neuromuscular physiology to medical, paramedical, and biological science students. The limited viability of the muscle is, however, a major drawback to this preparation, as many generations of students know to their cost. The gastrocnemius is too large a muscle for sufficient diffusion of oxygen and nutrients to occur from the outside; hence there is a quite rapid progressive deterioration of the preparation.

To maintain the muscle in a viable condition for a longer period requires an intact blood circulation. A blood-circulated gastrocnemius muscle preparation in a decerebrate frog was reported by Bremer more than 50 years ago (2). The relative insensitivity of amphibia to spinal shock raised the possibility that a similar blood-circulated preparation might be feasible in the spinal animal. We have investigated this possibility and have also examined the practicability of using such a blood-circulated preparation to demonstrate the actions of agents known to influence neuromuscular transmission.

Methods

Animals

All experiments reported here were performed on African clawed toads (*Xenopus laevis*) in the weight range of 20–36 g. Toads were stunned by a blow to the head. A fine scalpel blade was inserted into the spinal canal at the back of the skull severing the brain from the spinal cord. A blunt needle was then inserted through the hole made by the scalpel blade and pushed forward into the skull via the foramen magnum to destroy the brain. In our experience approximately three-fourths of the toads "survive" this procedure and recover from spinal shock within 10 min. The "surviving" spinal toads remained motionless unless touched but were capable of exhibiting strong withdrawal reflexes. Microscopic examination of the web of the foot by transmitted light revealed active blood circulation.

Operative Procedure (Figure 1)

An incision was made through the skin at the back of the ankle to expose the Achilles tendon. A thread was tied around the tendon above the sesamoid bone (the bone prevents the tie from slipping). The tendon was then cut below the bone (the body of the muscle was not exposed). A longitudinal incision was made through the skin of the dorsal side of the upper leg, and the sciatic nerve was exposed by pulling apart the muscle bundles. The sciatic nerve was freed from surrounding tissue, with care being taken to avoid damage to the femoral artery and vein that run alongside the nerve. A tight ligature was tied around the nerve high in the leg to prevent impulse transmission to or from the spinal cord. The sciatic nerve was separated from the underlying tissue by a small piece of Parafilm, and a small wad of absorbent cotton soaked in mineral oil was placed over the nerve to prevent drying.

Setting Up

The leg was fixed to a cork board via pins through the knee and ankle joints. The Achilles tendon was attached via the thread to an isotonic lever system (load 10 g; magnification ×10) that served to record muscle contractions on a kymograph drum (SRI student kymograph). Stimulating electrodes were placed in contact with the sciatic nerve so that it could be stimulated with square-wave pulses of 0.1-ms duration delivered by an SRI stimulator.

Drugs

The following drugs capable of influencing neuromuscular transmission were used in the doses indicated: tubocurarine chloride (Tubarine, Wellcome), 0.6 mg/100 g body wt; succinylcholine chloride

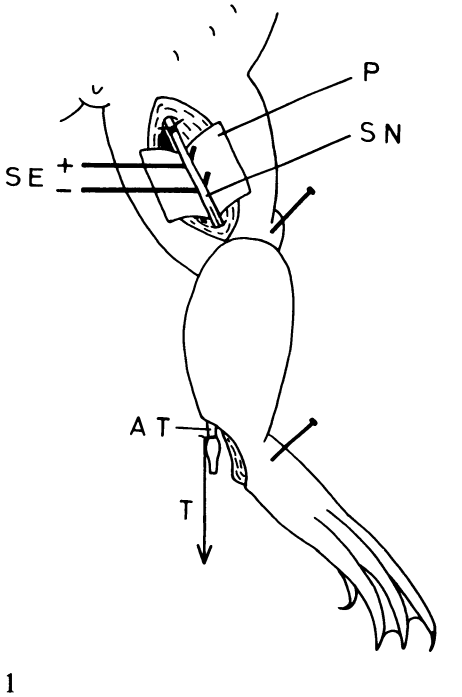

Figure 1
A dorsal view of right hindleg of a toad prepared for stimulation and recording. P, Parafilm; SN, sciatic nerve; SE, stimulating electrodes; AT, Achilles tendon; T, thread attaching tendon to lever system. (During the experiment exposed sciatic nerve was covered with a pad of absorbent cotton soaked in liquid paraffin.)

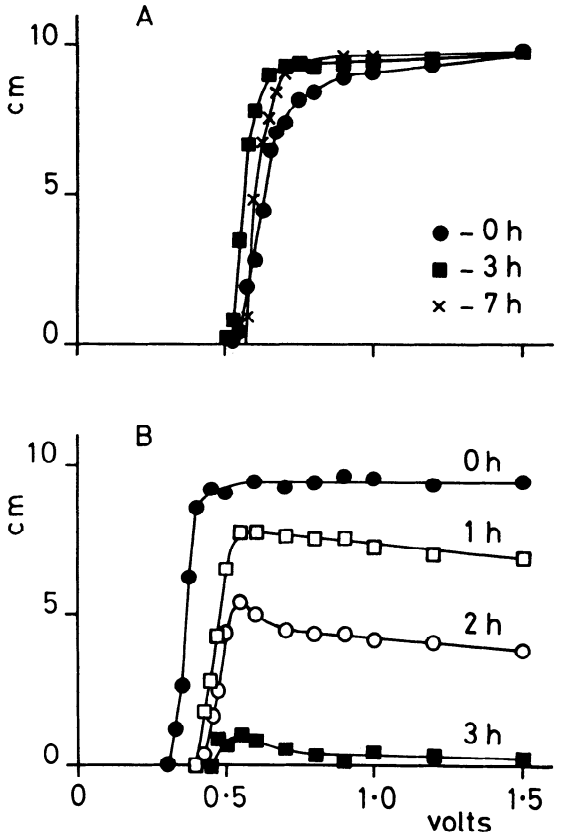

Figure 2
Graphs of contraction amplitude (as measured on kymograph paper) against stimulus voltage for single stimuli of 0.1-ms duration obtained immediately after setting up the preparation (0 h) and at times indicated thereafter. *A:* blood-circulated preparation in a spinal toad; *B*: isolated preparation.

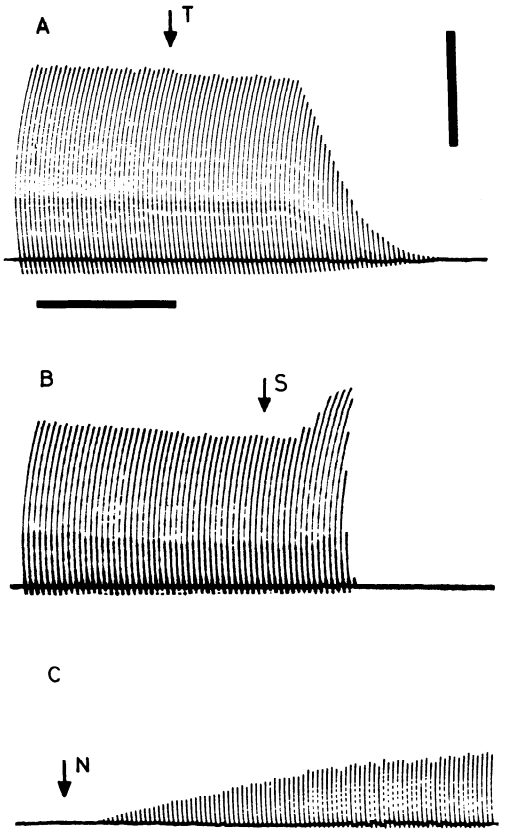

Figure 3
Contractions of a blood-circulated gastrocnemius muscle elicited by supramaximal stimuli (1.5 V) delivered to sciatic nerve at 20-s intervals. *A*: tubocurarine chloride was injected at "T." *B*: succinylcholine chloride was injected at "S." *C*: preparation in which neuromuscular transmission had been blocked by injection of tubocurarine chloride 30 min before start of record. Neostigmine methyl sulfate was injected at "N." *Horizontal black bar* represents 10 min and *vertical black bar* represents 5 cm on kymograph paper on all 3 traces.

(Scoline, Glaxo), 1.0 mg/100 g body wt; and neostigmine methyl sulfate (Prostigmin, Roche), 1.0 mg/100 g body wt. Intravenous injection is difficult in the toad; hence the drugs were administered by intramuscular injection at a site remote from the muscle under test. The most convenient site for intramuscular injection was found to be the gastrocnemius muscle of the opposite (unoperated) leg. From this site the drugs were absorbed into the bloodstream and carried by the circulation to the muscle under test.

Isolated Preparations

For comparison a small number of isolated sciatic nerve-gastrocnemius muscle preparations were dissected out from pithed toads and set up in the conventional manner (1), except that the sciatic nerve was placed on a piece of Parafilm and covered with absorbent cotton soaked in mineral oil so that the stimulation conditions would be similar to those in the blood-circulated preparation.

Results

Stimulus response curves to single 0.1-ms pulses delivered to the sciatic nerve at 20-s intervals were recorded from three blood-circulated preparations immediately after setting up (0 h) and at 1-h intervals thereafter. Figure 2 depicts typical data from one of these preparations showing the stimulus-response curves obtained at 0, 3, and 7 h. Although there were slight changes in the rising phase of the curve, there were no changes in the maximal amplitude during that time. (There was, however, some reduction in maximal amplitude by 8 h in all 3 preparations.) Figure 2*B* shows, for comparison, stimulus-response curves for an isolated preparation recorded at 0, 1, 2, and 3 h. At 0 h the shape of the stimulus-response curve and its maximal amplitude were similar to that seen in the blood-circulated preparation. Subsequent curves, however, showed the expected progressive deterioration of the preparation with time. By 1 h the maximal amplitude had declined by about 25%, by 2 h it had declined by more than 50%, and by 3 h it had declined by more than 90%.

If a series of single supramaximal (1.5 V) stimuli was delivered at 20-s intervals in a blood-circulated preparation, a series of gastrocnemius contractions of approximately equal amplitude were produced. Figure 3*A* shows the effect on such contractions of an injection of tubocurarine chloride at "T." There was a latent period of 9 min (presumably representing the time required for the tubocurarine to be absorbed from its injection site and carried by the circulation to the muscle

under test). This latent period was followed by a progressive reduction in contraction amplitude. The amplitude fell to zero after a further 11 min. Figure 3*B* shows the effect of injection of succinylcholine chloride at "S." After a shorter latent period of 3 min there was a potentiation of contraction amplitude due to the agonist activity of succinylcholine. This potentiation was rapidly superseded by depolarizing block of neuromuscular transmission, resulting in the abolition of the contractions. Figure 3*C* shows a preparation in which neuromuscular transmission had been blocked with tubocurarine administered 30 min previously. Neostigmine methyl sulfate was injected at "N." The anticholinesterase action of neostigmine increases the persistence of acetylcholine at the neuromuscular junction, allowing it to competitively overcome the blockade of transmission by tubocurarine and hence restore contractions.

Discussion

The blood-circulated sciatic nerve-gastrocnemius muscle preparation remained fully viable for 7 h with little change in the stimulus-response curve. This compares very favorably with the traditional isolated preparation in which appreciable deterioration occurred within 1 h. We thus propose that the blood-circulated sciatic nerve-gastrocnemius muscle provided a much more stable and long-lasting preparation on which to demonstrate the various aspects of neuromuscular physiology, such as force-velocity and length-tension relationships and summation and fusion of contractions, usually investigated in the progressively deteriorating isolated preparation (1).

An additional advantage of the preparation is that the presence of a functional blood circulation permits demonstration of how neuromuscular transmission can be influenced by various drugs. A drawback of the preparation is that the dissection involved, particularly the exposure of the sciatic nerve without damage to the femoral artery or vein, may be a little difficult for first-year students, if they lack previous experience of working with living tissues. Also some students may find it objectionable to dissect an animal which, although legally dead (the brain having been destroyed), still exhibits strong reflexes. For these reasons we feel that, for first-year students, it is better to use this preparation as a demonstration. We have successfully done this in the Physiology Department of the University of Zimbabwe.

During the prolonged latent periods while waiting for the injected drugs to act we have found it useful to maintain the interest of students by discussing with them the process of neuromuscular transmission and the expected actions of the drugs being used. *Xenopus laevis* has been used in this study as it is the usual laboratory amphibian in Zimbabwe. Preliminary experiments indicate, however, that the procedure works equally well using *Rana temporaria,* the more usual laboratory amphibian in the United Kingdom.

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Integration in Autonomic Ganglia

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In this paper I will discuss the evidence for neural integration in autonomic ganglia. This is not intended to be a comprehensive review of the literature on autonomic ganglia, a subject that has been reviewed on several occasions (9, 31, 48, 64, 72, 73, 74, 79, 80, 82). Integration in ganglia is discussed in a chapter by Blackman (3).

Historically, ideas about the autonomic nervous system have incorporated such concepts as "harmony" or "sympathy" between different organs in the body; hence, the term sympathetic nervous system (2, 81). The autonomic nervous system keeps the organ systems of the body in harmony with one another; making adjustments in blood flow, body temperature, water balance, and so forth to meet the needs of the *whole* organism. Therefore, in a general sense, we can appreciate that the adjustments effected by the autonomic nervous system require integration of information concerning the external and internal environments.

The autonomic ganglia are the final common pathway between the central nervous system and the effector organs. As such, they are the last point where outgoing signals can be modified. What is their involvement in integration of information and how does this affect the functions of the autonomic nervous system?

The integrative properties and capacities of autonomic ganglia are a manifestation of their organization as well as their anatomic, chemical, and functional complexity. Studies of all aspects of autonomic ganglia demonstrate that they have many attributes that equip them to integrate signals. These attributes will be described below and include the presence of subthreshold synaptic inputs, sensory input from effector organs, structural complexity, multiple innervation of individual neurons (convergence), the presence of several neurotransmitters, and complex interactions of multiple neurotransmitters. In short, autonomic ganglia are not simply points of relay and dispersion of impulses. Because of their relative simplicity, many of the cellular mechanisms whereby neural signals are fine-tuned are better understood in autonomic ganglia than in the central nervous system (CNS). Therefore integration in ganglia is a pertinent and compelling topic not only because such studies clarify our understanding of the autonomic nervous system but also because the findings can be applied to nervous systems in general.

Integration and Subthreshold Synaptic Potentials

Integration is the process whereby a neuron adds together all the excitatory and inhibitory signals that impinge on it and combines these converging signals into an output that takes into account all these signals. If a neuron is not integrating, it is functioning as a relay. Relay and integration are contrasted diagrammatically in Figure 1. As a relay, a neuron passes on all excitatory inputs as excitatory outputs (Figure 1*A*), and there would be no subthreshold postsynaptic potentials. On the other hand, if integration is occurring, at least some of the postsynaptic potentials are subthreshold excitatory or are inhibitory.

J. C. Eccles (25) suggested that certain autonomic ganglia do not merely relay information but that summation of subthreshold inputs may also occur. The presence of subthreshold synaptic potentials and summation of this was first confirmed with intracellular recordings by R. M. Eccles in 1955 (26), and since then this has been demonstrated in most sympathetic, parasympathetic, and enteric ganglia (5, 6, 15, 19, 33).

This is not to say that "relay synapses" do not exist in autonomic ganglia; the ciliary ganglion in birds (58), ganglia in the interatrial septum of frog heart (62), and most of the cells in the pelvic plexus of male guinea pig (4) are notable examples. The most common situation is that synaptic input to a ganglion is mixed, with some cells receiving only relay connections, some subthreshold only, and others both relay and subthreshold.

Sensory Input to Ganglia

Langley first designated peripheral autonomic nerve fibers as "preganglionic" and "postganglionic" when he found that applying nicotine to a ganglion would interrupt the flow of impulses through it in a central-to-peripheral direction (52, 53). It was this designation, while enlightening for its time, that perhaps has restricted conceptions of autonomic ganglia as relay centers in a solely efferent pathway in which the relays are nicotinic synapses. We now know that some sympathetic ganglia are innervated by sensory fibers coming from the effector organs. This adds a new dimension to the integrative properties of ganglia.

Direct evidence for sensory or afferent fibers making synaptic connections in sympathetic ganglia was first reported by Crowcroft and Szurszewski (15). Since then, there have been similar reports for other ganglia and other species. These are summarized in Figure 2. Tuttle and McCleary (75, 76) have found that distension of the carotid sinus inhibits ganglionic transmission in the superior cervical ganglion. This inhibition of transmission is mediated through firing in afferent fibers entering the ganglia. Excitatory synaptic potentials have also been recorded in the stellate ganglion and the middle cervical ganglion in response to stimulation of postganglionic fibers (6). This synaptic activity can be increased by lung inflation or an increase in the blood pressure in the aortic arch.

The nature of the postganglionic sensory input has been studied in the most detail in the prevertebral

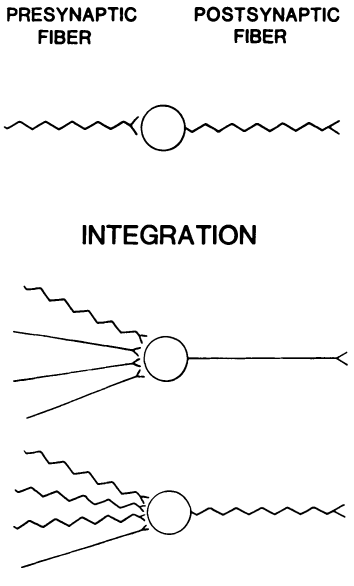

Figure 1

Diagrammatic representation of relay and integration functions in autonomic ganglia. *Upper panel*, labeled Relay, demonstrates a 1:1 correspondence between presynaptic firing and postsynaptic firing. There is no convergence of presynaptic fibers on ganglion cells. *Lower panel*, labeled Integration, demonstrates that only when sufficient number of presynaptic fibers are activated is there firing in the postganglionic neuron. Thus, when only 1 presynaptic fiber fires, there is no action potential in the postsynaptic cell; when 3 presynaptic fibers are activated, the postsynaptic cell is brought to threshold and fires. These presynaptic impulses could be summated spatially and/or temporally.

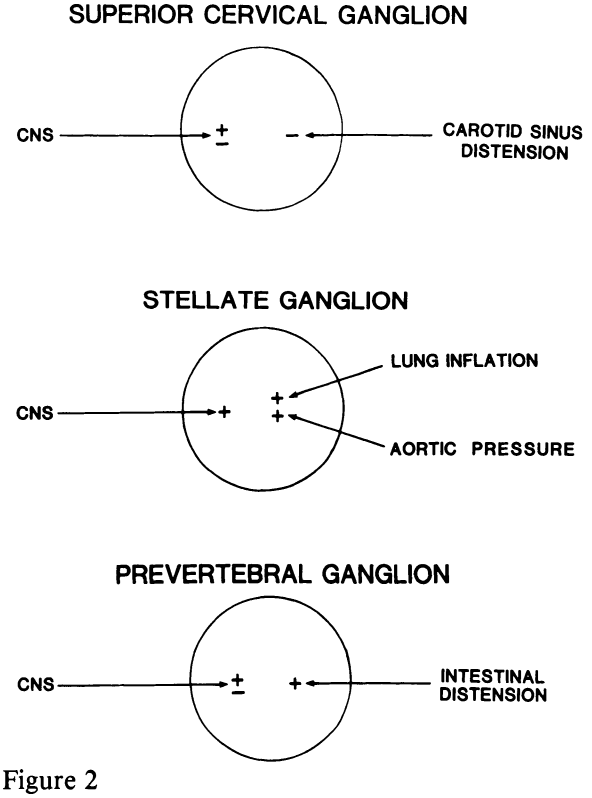

Figure 2

Diagram showing preganglionic and sensory information entering 3 different sympathetic ganglia. + and −, Excitation and inhibition of ganglionic cells, respectively. Derived from Tuttle and McCleary (75, 76) for superior cervical ganglion, Bosnjak and Kampine (6) for stellate ganglion, and Crowcroft and Szurszewski (15) and Kreulen and Szurszewski (44) for prevertebral ganglia.

ganglia. Stimulation of peripheral sensory fibers gives rise to both fast nicotinically mediated synaptic potentials and slow peptide-mediated excitatory synaptic potentials in the celiac, superior mesenteric, and inferior mesenteric ganglia of the guinea pig (14, 22, 45, 46) and the inferior mesenteric ganglion of the rabbit (41) and rat (42). In the cat renal ganglion, stimulation of renal nerves elicits in some cells synaptic potentials with a long latency, suggesting that an interneuron is involved in this sensory excitatory pathway (19). In the guinea pig and rat, the amount of excitatory synaptic input can be increased by intestinal distension (14, 42, 45, 46).

Ganglionic Reflexes

Because both the efferent and afferent limbs of a reflex arc are found in some sympathetic ganglia, there is a possibility for ganglionic reflexes, i.e., reflexes through ganglionic pathways only. This concept was suggested and studied as early as 1941 (49, 50). More recently, it has been tested in vitro in the guinea pig prevertebral ganglia with their connections to the colon (46). An increase in the activity of postganglionic sympathetic neurons inhibits contractions in the colon. When the intraluminal pressure in one segment of colon is raised, the motility in another segment of colon attached to the same ganglia is inhibited. This inhibition of one segment by distension in another can be eliminated by transection of the mesenteric nerves connecting the prevertebral ganglia to the colon.

This type of "peripheral" reflex also operates between the stomach and duodenum of the guinea pig (43). The ability of reflex pathways to mediate reflexes with other organs and their existence in other species remains to be examined.

Anatomy

Structural and histochemical studies support the concept that there exists in sympathetic ganglia the anatomic matrix for integration and that there are specific pathways for information flow. Three aspects will be discussed: *1)* structure of ganglia; *2)* organization of pathways within ganglia; and *3)* immunohistochemical evidence for the presence of neuropeptides.

Structure of Ganglia

The structure of sympathetic ganglion cells and their processes is complex, varies between species, and cannot be summarized easily (18, 28). In silver-impregnated preparations, ganglion cell processes, especially dendrites, are extremely numerous and vary in both size and length. These dendrites can course for some distance from the cell body, and the dendrites from several neurons can branch and form "pericellular nests" around adjacent neurons. In addition, dendrites from several ganglion cells converge into tracts or "dendritic glomeruli." The sympathetic ganglia of humans seem to be more complex than those of smaller mammals (28). The extremely complex structure of neurites within some ganglia suggests possibilities of interactions that to date have not been investigated.

The majority of sympathetic ganglion cells receive synaptic input from several fibers. The number of fibers innervating each cell varies within a ganglion as well as between different ganglia. Estimates of the ratio of preganglionic axons to ganglion cells have almost exclusively been made for the superior cervical ganglion (10, 65), and they have shown that the ratio may be as low as 1:4, much lower than the 1:32 often stated for sympathetic ganglia.

Because the number of ganglionic cells exceeds the number of preganglionic axons, there must be considerable branching of the axons. Indeed, in the superior cervical ganglion each individual axon is estimated to innervate 120 ganglion cells. Furthermore, each ganglion cell may receive more than one fiber from the same axon.

In addition to princtpal ganglion cells, sympathetic ganglia contain chromaffin-like cells, which are usually found in small clusters within the ganglia. These cells are smaller than the principal ganglion cells and give an intense fluorescent reaction for catecholamines. They have been called "small intensely fluorescent" (SIF) cells and can contain dopamine, epinephrine, or norepinephrine depending on the species and the ganglion (24, 26, 56). Like adrenal chromaffin tissue, some SIF cells also contain immunoreactivity to enkephalins (11). These SIF cells may function in some ganglia and in some species as interneurons (see below).

Organization of Ganglion Neurons

Topography or "regional distribution" of neurons has been demonstrated in some autonomic ganglia. In the superior cervical ganglion of the rat, neurons have been localized to certain regions of the ganglion depending on the postganglionic trunk into which they send their axons (8). A similar organization of cell bodies has been demonstrated in the stellate ganglion of the cat (60), where the acetylcholinesterase-rich cell bodies responsible for sweating in the forepaw are located in certain portions of the ganglia.

In addition to organization based on target organ, there is another kind of organization of neurons that is based on the source of preganglionic fibers. Specifically, there is "segmental dominance" of preganglionic input to neurons in the superior cervical and thoracic ganglia of the guinea pig (47, 55). According to these findings, each ganglion in the thoracic chain receives the most synaptic input from one segment of the spinal cord and progressively less input from the adjacent segments. Whether segmental dominance occurs in other ganglia is not known.

In the celiac plexus, neurons appear to be localized in the ganglia according to the nerve fibers into which their axons are routed (44, 83). In addition to this topography of postganglionic cell bodies, there is a partitioning of sensory fibers entering the ganglia from the periphery based on the region of the gastrointestinal tract from which the fibers arise. That is, sensory fibers from the proximal parts of the colon synapse on a greater percentage of neurons in the more rostrally located celiac ganglia than in the more caudal superior mesenteric or inferior mesenteric ganglia. In like manner, sensory fibers from the caudal colon synapse on a greater majority of tested neurons in the inferior and superior mesenteric ganglia than in the celiac ganglia.

Presence of Neuropeptides

One of the most active areas of research on autonomic ganglia recently has been the localization of neuroactive peptides using immunohistochemistry. This has sparked considerable interest in determining the role they play in ganglionic transmission. Several peptides have been found to exist in either ganglion cell bodies or

fibers or both (Table 1). Some peptides are found to coexist with norepinephrine or with other peptides within the same neuron.

The prevertebral ganglia not only contain several neuropeptides, but the neurons are regionally distributed based on the type of neuropeptides and neurotransmitters they contain. For example, in the superior mesenteric and celiac ganglia of the guinea pig, neurons can be divided into four types: those that contain *1*) norepinephrine only, *2*) vasoactive intestinal peptide (VIP) only, *3*) norepinephrine and somatostatin, and *4*) norepinephrine and avian pancreatic polypeptide. Each of these types of neurons is located in a different part of the ganglia. In addition, VIP fibers impinge only on the norepinephrine- and norepinephrine-somatostatin-containing neurons. This suggests that these neuroactive substances could influence only certain pathways or only a particular group of neurons.

Interactions of Neuroactive Substances

The crucial question that remains is how the different pathways and neuroactive substances interact with one another. The interactions of neuroactive substances within the ganglia form the basis of their integrative properties. Likewise, the integrative capacity of a multiple transmitter system is more than that of a single transmitter system.

When presynaptic fibers are stimulated, several synaptic potentials of different durations and time courses are recorded in many autonomic ganglia. These different postsynaptic potentials are a result of the release of more than one transmitter or, as in the case of acetycholine, two effects of the same transmitter on the postsynaptic membrane. Furthermore, some substances have both presynaptic and postsynaptic effects.

No neurotransmitter exemplifies the possible range of multiple effects better than acetylcholine, which produces a nicotinic fast excitatory postsynaptic potential (EPSP), a muscarinic slow inhibitory postsynaptic potential (IPSP), a muscarinic slow EPSP (11), and muscarinic presynptic inhibition of acetylcholine release (38). Furthermore, it also mediates via muscarinic receptors a release of catecholamines from SIF cells in the rabbit superior cervical ganglion (55).

Catecholamines are found within ganglion cells and with SIF cells (77) and may also contribute to the integrative properties; however, the effects of catecholamines on autonomic neurons are complex and may be dependent on both the species and ganglion (30). In the rabbit superior cervical ganglion (55), dopamine appears to produce a slow IPSP in ganglion neurons after being released from SIF cells by acetylcholine acting on muscarinic receptors. On the other hand, in the bullfrog sympathetic ganglia (20), the mammalian parasympathetic vesical ganglia (29), and the mudpuppy cardiac ganglion (32), the slow muscarinic IPSP appears to be mediated by acetylcholine acting directly on ganglion neurons in a catecholamine-independent pathway. In mammalian sympathetic ganglia, intracellular recordings show that adrenergic agonists cause variable changes in the membrane potentials of principal neurons (34) and that they act presynaptically to inhibit the release of acetylcholine (13, 70).

Table 1
Neuropeptide Immunoreactivity in Sympathetic Ganglia

	Ganglion Cell Bodies	Fibers
Substance P	+	+ +
Vasoactive intestinal peptide	+	+ + +
Somatostatin	+ + +	+
Enkephalin	–	+
Avian pancreatic polypeptide	+ +	+
Neurotensin	–	+

Neuropeptides

Not all of the potentials recorded in autonomic ganglia are mediated by acetylcholine and catecholamines. In the bullfrog sympathetic ganglia, a luteinizing hormone-releasing hormone-like peptide appears to mediate a slow depolarizing response (35), and in guinea pig myenteric ganglia, long time-course depolarizations may be mediated by serotonin or substance P (37, 38).

As described above, several neuroactive peptides have been found in mammalian sympathetic ganglia, and two of these peptides, substance P and enkephalin, have effects on ganglionic function that are capable of altering the integrative properties of the ganglia.

Substance P

Substance P, either administered or released from nerves, produces a long-lasting (seconds to minutes) depolarization of neurons in the guinea pig inferior mesenteric ganglia (22, 24, 48). During the depolarization the excitability of the neurons is increased both because the membrane potential is closer to threshold and because the input resistance is increased. Thus synaptic potentials that would normally be subthreshold may give rise to action potentials if they arrive during the slow depolarization.

Histochemical studies (17, 59) and nerve stimulation experiments (22, 40) indicate that the substance P is contained in primary sensory fibers that apparently pass through the ganglia. The sensory modality that activates these pathways is not known, although a noncholinergic mechanoreceptor pathway from the colon has recently been described (70). Thus there are two sensory pathways converging in the prevertebral ganglia, the cholinergic mechanoreceptor pathway and the substance P pathway. Both pathways have an excitatory influence on ganglionic neurons.

Enkephalins

Preganglionic nerve fibers having immunoreactivity for enkephalins are found in inferior mesenteric ganglia of the guinea pig (16, 39, 40). Enkephalins released from these fibers or applied to the ganglion decrease the release of acetycholine and substance P (36, 39). These effects of enkephalins occur without any direct effect on ganglionic neurons. This enkephalinergic pathway would be a means whereby impulses from the central nervous system would suppress excitatory synaptic activity from both preganglionic (central) and sensory pathways.

Presynaptic inhibition of transmitter release appears to be a mechanism with several pharmacological "pathways," and several other neuroactive substances have been found to have presynaptic inhibitory effects on the release of acetylcholine in sympathetic ganglia. These include prostaglandins (21), 5-hydroxytryptamine (23),

adrenergic agonists (69), and muscarinic agonists (38). It may be that an important inhibitory influence on sympathetic ganglia is the inhibition of excitatory neurotransmitter release.

Implications for Function of Autonomic Nervous System

Do the many integrative properties of autonomic ganglia have any ramifications as to function of the autonomic nervous system? This is a subject that for the most part is speculative. In situations such as the "fight-or-flight response" it is difficult to imagine what role integration of signals by ganglia might have. On the other hand, this emergency response of the autonomic nervous system is only one aspect of the control of visceral function. The role of the autonomic ganglia in non-emergency situations may represent a more important component of their overall function.

Perhaps the clearest way to represent ganglionic function would be to think of at least two functional pathways in the ganglia, the relay pathway and the integration pathway. There is some evidence for this. For example, in both sympathetic and parasympathetic ganglia, some neurons receive subthreshold input, whereas others are relay neurons without subthreshold input. Furthermore, in some ganglia the neurons that control different functions can be activated separately. A single neuron could be in both pathways depending on which presynaptic fibers and/or transmitters were used. During a fight-or-flight response it is primarily the relay pathway that is activated. In this pathway, the various modulating influences on ganglionic neurons would have only weak influences on transmission, since there is probably a large safety factor for transmission in the relay pathways. It would be disadvantageous for the organism to have transmission failure in this situation.

The functions and behaviors of the integration pathway would be quite different. Ganglionic neurons in this pathway would be influenced not only by central preganglionic fibers but also by peripheral sensory fibers, especially in light of the fact that neurons in some ganglia receive more sensory that central input. Furthermore, modulating influences would play a much more important role than in the relay pathway because the safety factor for synaptic transmission would be very small. Thus, in the integration pathway, the integration of signals from several sources would ensure that outgoing impulses from autonomic ganglia would reflect not only the input from the central nervous system but also the influence of the effector organs.

Activity in or operation of the integration pathway would bestow an amount of specificity to the postganglionic outflow. How this could be achieved in abdominal sympathetic (prevertebral) ganglia is diagrammed in Figure 3. The principal ganglionic neurons are shown receiving inputs from excitatory preganglionic fibers and excitatory sensory fibers. The excitatory preganglionic fibers release acetylcholine, which mediates a nicotonic fast EPSP and a muscarinic slow IPSP. For simplicity only the former is considered in this example. The sensory fibers could release both acetylcholine and substance P, which depolarize the neurons, and the preganglionic inhibitory fibers could release enkephalins, which would inhibit the release of acetylcholine from both central and sensory nerve endings. Even though all the preganglionic fibers in this diagram are activated, not all of the postganglionic neurons are brought to firing threshold. In this example, the neuron that innervates the small intestine is the only one that fires. It does so because it receives the additional excitatory input from sensory fibers coming from the stomach that are activated by distension of that organ. Furthermore, the excitatory synaptic input to this cell is not diminished by the preganglionic enkephalinergic fibers. In this way, the outflow from this ganglion is "made specific" by the convergent input integrated by the neurons. An additional amount of specificity could be conferred on this system by the topography of a ganglion with respect to the source of sensory input or neurotransmitter content of both afferent and efferent fibers. Furthermore, because of segmental dominance of preganglionic input, activation of only certain levels of the spinal cord could contribute even more specificity to the outflow. Thus, in the integration pathways, the postganglionic outflow to effector organs can be regulated by activity in effector organs and can be organ specific.

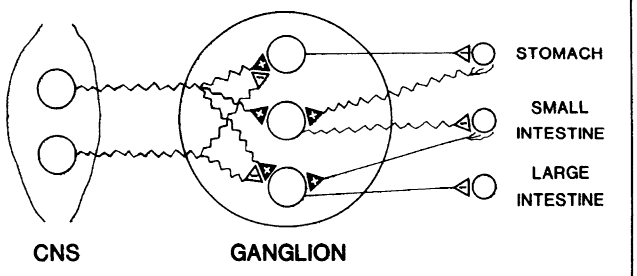

Figure 3
Diagrammatic representation of integration in a prevertebral sympathetic ganglion innervating 3 different abdominal organs. *Jagged lines* represent neurons that are activated and *straight lines* inactive neurons. Two types of preganglionic fibers are shown coming from the central nervous system (CNS): excitatory cholinergic fibers (+) that synapse on ganglion neurons and inhibitory (−) fibers (possibly enkephalinergic) that impinge on the cholinergic fibers. Excitatory sensory fibers are indicated by the branched terminals in the stomach and small intestine; only one of these is activated, that from the stomach. The only neuron that receives sufficient excitatory synaptic input to be activated is the one innervating the small intestine. This occurs because the neurons integrate input from multiple sources in systems using multiple neorotransmitters. For more details, see text.

Summary

Recent advances in our knowledge of autonomic ganglia support the concept that the structural and functional elements of neural integration are present in the ganglia. These elements include subthreshold synaptic potentials, convergence of efferent and afferent presynaptic fibers, topography of ganglia, complexity of structure, and multiple neurotransmitters and neuroactive substances. An understanding of the contribution of each of these elements to the function of autonomic ganglia and the autonomic nervous system will require careful examination of each in the context that the ganglia are the final modifiers of neural signals

to the viscera. Most of these pieces of information have not been fitted to the puzzle.

Future studies on autonomic ganglia will relate to both their simplicity and their complexity. Autonomic ganglia have been and will continue to be used as models of the central nervous system, as a means to better understand the basic mechanisms that occur in the far more complex central nervous system. The role of neuroactive peptides and their effects on ganglionic function will continue to be of great interest. Knowledge of the organization of neurons and pathways within the ganglia and the implications of this organization for ganglionic transmission and integration will develop rapidly. Finally, the use of autonomic ganglia for developmental studies will continue; especially interesting will be the study of the factors that influence the phenotypic expression of neuronal properties. All of these studies will contribute to our understanding of the function of autonomic ganglia and will amplify the knowledge we already have of the importance of neural integration in the autonomic ganglia for the function of the autonomic nervous system.

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A Simple ECG Training Device

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Prior to taking meaningful electrocardiographic (ECG) records from animals or humans, one must understand: *1*) the meaning of the P, QRS, and T waves and *2*) the meaning of the leads. The first is easily learned from the physiological principles of excitation and recovery; the second is often more difficult to conceptualize. The simple ECG training device described herein provides direct experiential contact with the concept of cardiac axis and lead direction.

The training device (Figure 1) consists of a circular transparent jar of any convenient size with a transparent cover. The radius of the jar should be at least five times the length of the dipole. The jar is filled with dilute saline (0.6 or 0.9 %) to simulate the body tissues and fluids. The electrodes [right arm (RA), left arm (LA), and left leg (LL)] consist of threaded brass rods (8-32), available from most hardware stores, mounted with nuts to the transparent cover at the apices of an equilateral triangle. After mounting, the tips (T) of the rods are cleaned with steel wool and tinned with solder for a length of 1 inch to create the electrode surface. Each rod is insulated to within about 5 mm of the tip with a piece of plastic or shrink tubing. Prior to placing the insulation on the rods, a thin coat of RTV, a silicone rubber, is applied to prevent saline from migrating up the threads under the insulation. The rod electrodes need only extend to half the depth of the jar. The exposed tinned distal 5-mm portion constitutes the electrode surface (T).

The heart is simulated by a dipole (see below) centrally located at the level of the electrodes and driven by a stimulator with an isolated output. The dipole can be oriented to any angle with respect to the three electrodes. The cardiac dipole is made from two threaded (8-32) brass rods that are as long as the RA, LA, and LL electrode rods and are mounted a (about 1 inch apart) on a plastic crossarm using nuts as shown on the left of Figure 1. The distal ends of the threaded rods are cleaned with steel wool and tinned for a length of about 1 inch. The rods are coated lightly with RTV silicone cement; then the insulating tubing is applied as for the recording electrodes, leaving the last 5 mm bare to constitute the poles of the dipole (T). The crossarm has a hole in the center for a plastic tube, which is cemented to it and forms the axle that passes through the cover of the jar. Two plastic collars are slipped on the plastic axle, above and below the vessel cover, and secured by setscrews. On the lower collar, an arrow is affixed appropriately to identify the orientation of the dipole. Thus the axle can be rotated to place the dipole in any desired orientation with respect to the various leads. Two stranded wires are soldered to solder lugs bolted to the threaded dipole rods and led up the center of the plastic tube axle.

The only critical feature of the ECG trainer is the use of a stimulator with an isolated output to excite the dipole. Ground-referenced stimulators may not produce the potentials predicted by the orientation of the dipole with respect to the electrode axis. A convenient dipole driver is the model SIU-5A Stimulus Isolateds Unit connected to the model S44 stimulator (Grass Instrument, Quincy, MA) or a model SI-10 stimulator (Narco BioSystems, Houston, TX); other stimulators with the same output characteristics can be used. A stimulus frequency of 1.5/s (equivalent to a heart rate of 90 beats/min) and a stimulus duration of 120 ms (simulating QRS duration) are convenient. With 0.9% saline, a simulator output of about 2 V will provide about 1 mV across a pair of electrodes when the dipole axis is parallel to an electrode pair.

The cover of the jar should carry labels for the three limb terminals (RA, LA, and LL). The augmented V (aV) leads can be synthesized easily by installing terminals midway between the RA, LA, and LL(F) terminals on the cover of the jar and connecting 47,000-Ω resistors from each augmented lead terminal to the two adjacent

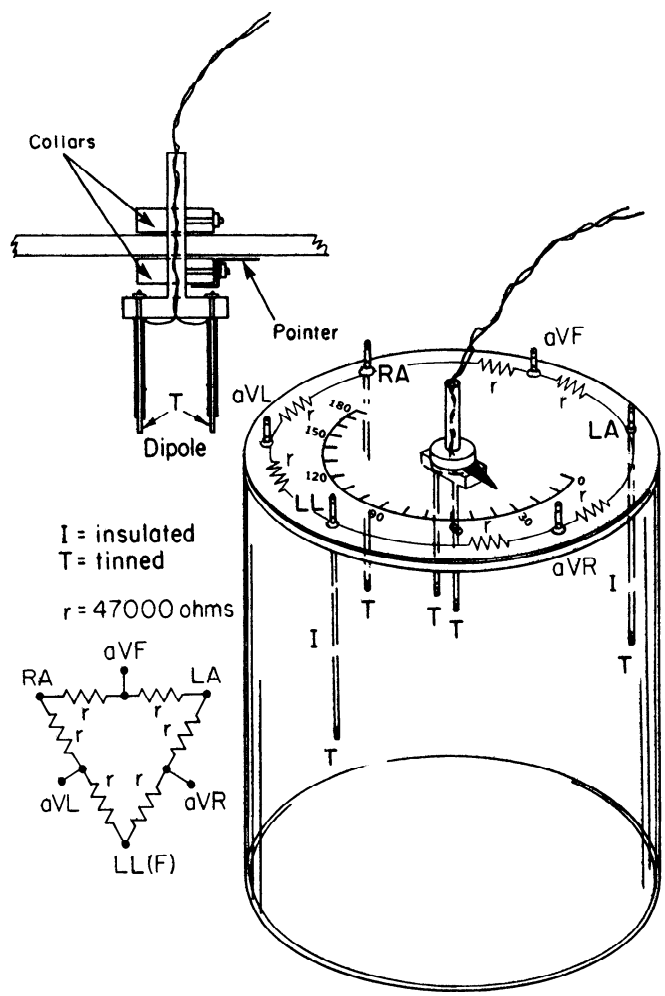

Figure 1
ECG training device, consisting of a driven dipole in a volume conductor (saline) in which 3 limb and augmented leads are placed.

Dedicated to Hebbel E. Hoff, who originated the idea of the training device.

Table 1
Orthogonal Leads

Angle	Lead	Angle, °	Lead
0	aVF	210	III
30	III	240	aVL
60	aVL	270	I
90	I	300	aVR
120	aVR	330	II
150	II		
180	aVF		

Table 2
Orthogonal Angles and Leads

Lead Designation	Orthogonal Angles, °	Orthogonal Leads
I	90 and 270 (—90)	aVF
II	150 and 330 (—30)	aVL
II	30 and 210	aVR
aVR	120 and 300	III
aVL	60 and 240	II
aVF	0 and 180	I

limb-lead terminals, as shown in Figure 1. To prevent moisture from condensing on the resistors, each should be placed in plastic tubing (as for the limb and dipole electrodes). Thus the aVL terminal is at the midpoint of 47,000-Ω resistors connected to RA and LL(F); the aVF terminal is at the midpoint of two 47,000-Ω resistors joined to the RA and LA terminals; and the aVR terminal is at the midpoint of the two 47,000-Ω resistors connected to the LL(F) and LA terminals.

A 30°, 60°, 90°, etc. degree scale should be placed on the cover above the tip of the arrow that identifies the orientation of the dipole. Locating these points is easy by recording from a lead that is perpendicular to the dipole. For example, with the dipole driven by the stimulator, the 0° point is located by finding the dipole orientation for a null in lead aVF. Such a lead is a perpendicular or orthogonal lead. Similarly for the 30° point, the null occurs in lead III. Table 1 presents the leads that provide a null for the different angles in 30° increments. Electrical identification of the angles permits very accurate location of the various angles.

One, two, or three channels of ECG can be recorded simultaneously. If a multichannel recording is used, care must be exercised to calibrate all channels to the same recording sensitivity. Figure 2 illustrates a three-channel recording as the dipole is rotated from 0° (RA-LA reference) through 90° to 180°. The expected amplitudes and polarities are clearly displayed. Table 2 lists the leads that are orthogonal to the various angles and leads.

A more sophisticated version of this training device (1) has been used for about 15 years as a demonstration

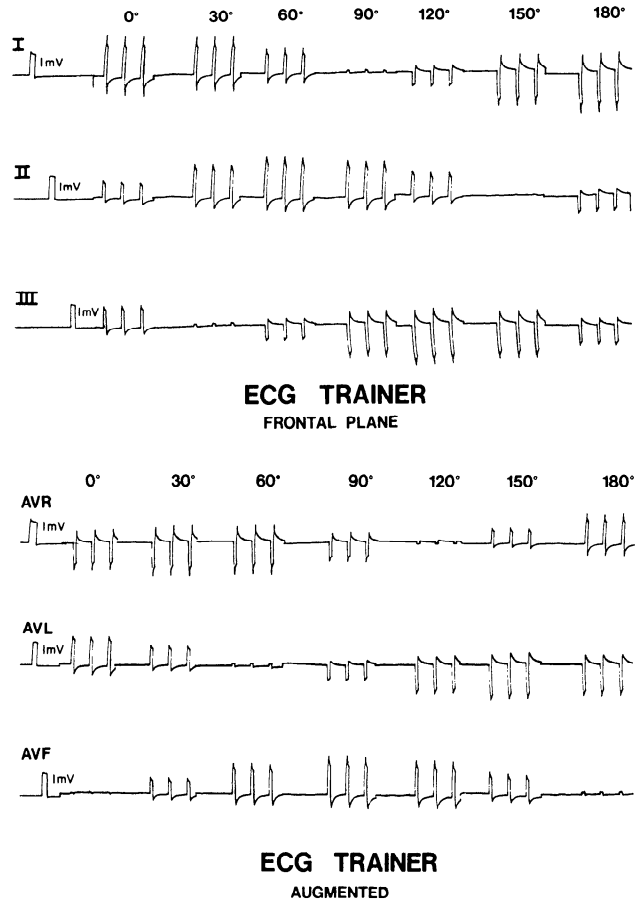

Figure 2
Amplitudes in 3 limb leads (*top*) and augmented leads (*bottom*) as the dipole is turned in 30° increments from 0 to 180°.

device at Baylor Medical College and for about 8 years at Purdue University. With the wide availability of stimulators with isolated output circuits, it is both easy and inexpensive to add this trainer to the laboratory exercises, providing excellent orientation for the ECG, before encountering animals and human subjects. The resourceful teacher will be able to devise useful problems for students to solve and prove the results experimentally with the trainer. For example, the student can be requested to identify the vector angles that produce a null or maximum in a particular lead or leads, or alternately, the vector angles in which the same amplitudes are obtained in two leads.

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A Microprocessor Analog Simulation of the Operation of Countercurrent Multiplier Systems

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The operation of the countercurrent multiplier system in the ascending (AHL) and descending (DHL) loops of Henle can be very difficult to visualize. The principle is a simple one, however, and it has very powerful physiological consequences.

Presenting the concept in more than a memorizable format is difficult, because we tend to restrict what the student can do with the principle itself. We want them to see what we think is true now. It is possibly true that the principle is more important than our immediate applications for it. At any rate it is "working with principles" that makes physiology "fun."

The principle of countercurrent multiplication is powerful, even if all of the details of its application are not clear (2–4). It now seems likely that some element of active pumping is involved in the establishment of the impressive gradients of osmotic pressure between the renal cortex and medulla (3). It is interesting to remember that pumping was prohibited by Cushny (1) in his 1926 "modern theory of renal function." It is a matter of some interest to allow the student to experiment with where the various pumps could be placed and what effect changing the rate of pumping might have on the overall process. It is also useful for them to be able to change the effective length of a loop and visualize the consequences of this action. It is the principle that we want to illustrate rather than a recitation of current belief.

The various models for countercurrent multipliers, simulated here, are constructed as arrays in the memory of the microprocessor. The name of the array represents volume, concentration, or quantity of solute at a particular level in the renal medulla. The subscript of the array represents its level in the medulla.

The arrays can be made to behave as successive levels of tubule and interstitium during the descent of tubular fluid through the renal medulla; followed by its movement back toward the cortex, wherein a dilution of the urine occurs.

At each stage the arrays can be moved according to the algorithm of the model being simulated. When the process reaches a steady state the contents of the arrays can be viewed as an analog of renal function. The process is short, direct, and easy to visualize.

The advantage of using arrays is that it is easy to remember that arrays starting with a "C," "Q," or "V" represent concentration, amount of solute, or the volume of fluid flowing through that region, respectively. Thus any Q term is solved for as the product of a C × V. It is easy to think your way through the program in this manner.

This microprocessor model simulates the behavior of the AHL and DHL, where pumps, under the control of the user, shift solute from the AHL or the DHL into the renal interstitium.

The pumps may or may not exist in our current dogma of renal physiology; it is the principle that we are attempting to illustrate. It is interesting to see what would happen with a single pump located in the DHL and no pump in the AHL. Viewing the result makes one understand why this cannot ever be; it generates a gradient of concentrations in the wrong direction! Most students will probably conclude, after exercising this model, that only one pump is needed with its location in the AHL.

At the end of each shift of solute the equilibrium concentrations are calculated, and then water is shifted to satisfy osmotic demands.

It is assumed that the DHL is very permeable to water and that the AHL is effectively waterproof in its thick section. We are not attempting to illustrate either the anatomy or the action of the thin ascending loop here.

The length of the loop of Henle can be controlled as well as the rate of washout of trapped solutes in the interstitium of the kidney. This is one of the principles of the system that is being illustrated.

The rate of washout represents the loss of solutes by simple diffusion from medulla to cortex and into the blood of the vasa recta as it moves into and out of the medulla. The model presented here handles this removal of solute at each level in proportion to the concentration that is present. The model allows setting this rate as a fraction so that the effect on the establishment of a new steady state can be visualized. The physical nature of washout as represented here is unimportant in terms of the principle being illustrated. Although the hairpin loop shape of the vasa recta tends to minimize the loss of solutes from the medulla, solutes are lost from the medulla into the vascular system. These losses are probably in proportion to the concentrations present. They are handled in this fashion by the model which does not provide any further details for this action.

The simulation begins with global equilibrium: all concentrations and flow rates are the same. Then the cycles of transfer of solute begin, followed by osmotic shifts and some washout, when this parameter is greater than zero. With reasonable levels of washout a new steady state is quickly established, as can be observed in the cyclic display of array contents. If both possible pumps are set to zero, then there are no changes that can be observed, and the array's stay as they were.

The model is direct and illustrates the following factors: *1*) the effect of the length of the loop of Henle on the concentration gradient developed from cortex to medulla; *2*) the effect of the various rates of theoretical pumping on the concentration and volume of the tubular fluids; *3*) the influence of the location of the pumps in the AHL or DHL or both (results here can be surprising); *4*) the effect of the rate of washout of the ac-

cumulated solutes in the renal interstitium; *5*) how the decreasing osmotic concentrations associated with fluid movements from medulla to cortex, in the AHL, results in smaller osmotic concentration differences between the tubular lumen and the renal interstitium (the countercurrent mechanism spreads a small gradient over a large distance); and *6*) the "multiplier effect," which can be observed with each cycle of the model's arrays through the renal medulla.

The present model is concerned with the multiplying power of countercurrent mechanisms. It does not deal with the events thought to occur when the fluids descend through the collecting ducts in the presence or absence of antidiuretic hormone. However the model could be quickly and easily modified to include these factors.

Equations

There are no true equations present in this model except for that used to calculate osmotic balance in line 780 and the one used to plan a level of interstitial washout of solute in lines 910 and 920. Instead there are a series of assignment statements.

The algorithm is one of "taking" from one array assignment and "putting" into another. The cyclic process begins in line 640 where new glomerular filtrate is added to the system before a new cycle is started.

The algorithm simulates how the system moves from uniform concentrations of 300 mosmol/l and flow rates of 24 ml/min to a new steady state associated with the activity of pumps 1 (DHL), 2 (AHL), a particular washout rate, and a fixed length of Henle's loop.

Major Program Variables

P1	pump rate for the DHL: when set to zero this pump vanishes
P2	pump rate for the AHL
WASH	rate of washout of the solutes in the interstitium
L	length of the loop of Henle; each modifier (I) represents a level in the renal medulla
QDHL (I)	quantity of solute in the arrays of the DHL
QINS (I)	quantity of solute in the arrays of the interstitium
QAHL (I)	quantity of solute in the arrays of the AHL
VDHL (I)	volume of fluid flowing through an array of the DHL
VAHL (I)	volume of fluid flowing through an array of the AHL
DHL (I)	osmotic concentration of the fluid in the arrays of the DHL
CINS (I)	osmotic concentration of the fluid in the arrays of the renal interstitium
CAHL (I)	osmotic concentration in the arrays of the AHL
VINS (I)	volume of the arrays of the renal interstitium

The units are milliosmoles per liter (mosmol/l for concentrations and milliliters per minute (ml/min) for the flow rates; solutes are expressed as the product of the flow rate times the concentration. Initial values of concentration are set at 300 mosmol/l and 24 ml/min.

Figure 1
Sample Run of CCURRENT.BAS Program

```
SIMULATE THE COUNTER CURRENT MULTIPLIER IN THE KIDNEY


ENTER THE DESCENDING PUMP MULTIPLIER (0-460) 0
ENTER THE ASCENDING PUMP MULTIPLIER 230
ENTER THE INTERSTITIAL WASHOUT RATE (0-1) 1
ENTER LENGTH OF THE LOOP OF HENLE (5-15) 5
 0  XX 300.00    24.00 XX    300.00      XX 300.00 24.00 XX
 1  XX 300.00    24.00 XX    300.00      XX 300.00 24.00 XX
 2  XX 300.00    24.00 XX    300.00      XX 300.00 24.00 XX
 3  XX 300.00    24.00 XX    300.00      XX 300.00 24.00 XX
 4  XX 300.00    24.00 XX    300.00      XX 300.00 24.00 XX
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
The higher numbers move down into the medulla
Watch for stability in the values for the new steady state
Present Pump Multiplier Values are:
Washout rate = 1                          Descending Pump = 0
                                          Ascending  Pump = 230
 Depress the space bar - to stop the program - restart with RUN

                    INITIAL RUN ABOVE
                    STABLE RUN BELOW
                   SHORT LOOP OF HENLE
      CONC DHL     VOL DHL     CONC INS      CONC AHL VOL AHL
 0  XX 309.58    23.26 XX    309.58      XX 293.08 20.64 XX
 1  XX 319.32    22.55 XX    319.32      XX 304.22 20.64 XX
 2  XX 329.12    21.88 XX    329.12      XX 315.37 20.64 XX
 3  XX 338.95    21.24 XX    338.95      XX 326.51 20.64 XX
 4  XX 348.79    20.64 XX    348.79      XX 337.65 20.64 XX
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
The higher numbers move down into the medulla
Watch for stability in the values for the new steady state
Present Pump Multiplier Values are:
Washout rate = 1                          Descending Pump = 0
                                          Ascending  Pump = 230
 Depress the space bar - to stop the program - restart with RUN


SIMULATE THE COUNTER CURRENT MULTIPLIER IN THE KIDNEY

ENTER THE DESCENDING PUMP MULTIPLIER (0-460) 0
ENTER THE ASCENDING PUMP MULTIPLIER  230
ENTER THE INTERSTITIAL WASHOUT RATE (0-1) 1
ENTER LENGTH OF THE LOOP OF HENLE (5-15) 15

                STABLE VALUES PRINTED BELOW
                    LONG LOOP OF HENLE
      CONC DHL     VOL DHL     CONC INS      CONC AHL VOL AHL
 0  XX 309.58    23.26 XX    309.58      XX 232.63 16.12 XX
 1  XX 319.32    22.55 XX    319.32      XX 246.90 16.12 XX
 2  XX 329.12    21.88 XX    329.12      XX 261.16 16.12 XX
 3  XX 338.95    21.24 XX    338.95      XX 275.43 16.12 XX
 4  XX 348.79    20.64 XX    348.79      XX 289.70 16.12 XX
 5  XX 358.63    20.08 XX    358.63      XX 303.97 16.12 XX
 6  XX 368.45    19.54 XX    368.45      XX 318.23 16.12 XX
 7  XX 378.26    19.03 XX    378.26      XX 332.50 16.12 XX
 8  XX 388.06    18.55 XX    388.06      XX 346.77 16.12 XX
 9  XX 397.85    18.10 XX    397.85      XX 361.04 16.12 XX
10  XX 407.63    17.66 XX    407.63      XX 375.31 16.12 XX
11  XX 417.39    17.25 XX    417.39      XX 389.57 16.12 XX
12  XX 427.15    16.86 XX    427.15      XX 403.84 16.12 XX
13  XX 436.90    16.48 XX    436.90      XX 418.11 16.12 XX
14  XX 446.64    16.12 XX    446.64      XX 432.38 16.12 XX
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
The higher numbers move down into the medulla
Watch for stability in the values for the new steady state
Present Pump Multiplier Values are:
Washout rate = 1                          Descending Pump = 0
                                          Ascending  Pump = 230
 Depress the space bar - to stop the program - restart with RUN


SIMULATE THE COUNTER CURRENT MULTIPLIER IN THE KIDNEY


ENTER THE DESCENDING PUMP MULTIPLIER (0-460) 0
ENTER THE ASCENDING PUMP MULTIPLIER 460
ENTER THE INTERSTITIAL WASHOUT RATE (0-1) 1
ENTER LENGTH OF THE LOOP OF HENLE (5-15) 15

            STABLE VALUES FOR HIGHER PUMP RATE

      CONC DHL     VOL DHL     CONC INS      CONC AHL VOL AHL
 0  XX 319.17    22.56 XX    319.17      XX  24.85 12.07 XX
 1  XX 338.93    21.24 XX    338.93      XX  62.96 12.07 XX
 2  XX 358.95    20.06 XX    358.95      XX 101.07 12.07 XX
 3  XX 379.04    19.00 XX    379.04      XX 139.18 12.07 XX
 4  XX 399.11    18.04 XX    399.11      XX 177.30 12.07 XX
 5  XX 419.12    17.18 XX    419.12      XX 215.41 12.07 XX
 6  XX 439.06    16.40 XX    439.06      XX 253.52 12.07 XX
 7  XX 458.93    15.69 XX    458.93      XX 291.63 12.07 XX
 8  XX 478.72    15.04 XX    478.72      XX 329.74 12.07 XX
 9  XX 498.46    14.44 XX    498.46      XX 367.85 12.07 XX
10  XX 518.15    13.90 XX    518.15      XX 405.96 12.07 XX
11  XX 537.79    13.39 XX    537.79      XX 444.07 12.07 XX
12  XX 557.40    12.92 XX    557.40      XX 482.18 12.07 XX
13  XX 576.97    12.48 XX    576.97      XX 520.29 12.07 XX
14  XX 596.51    12.07 XX    596.51      XX 558.40 12.07 XX
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
The higher numbers move down into the medulla
Watch for stability in the values for the new steady state
Present Pump Multiplier Values are:
Washout rate = 1                          Descending Pump = 0
                                          Ascending  Pump = 460
 Depress the space bar - to stop the program - restart with RUN
```

Note that user input is underlined

Program Listing

```
10 '              CCURRENT.BAS
20 '
30 'Robert W. Rasch
40 'Box 19,780A
50 'Department of Physiology
60 'Quillen-Dishner College of Medicine
70 'Johnson City, TN 37614
80 '(615) 928 6426 x235
90 '
100 'An Analog Simulation of the Counter
110 'Current Multiplication System as it
120 'might apply to the Ascending and
130 'descending loop of Henle.
140 '
150 'Variable pump rates in two locations are
160 'supplied. Variable washout rates that
170 'are in proportion to the length of
180 'the loop of Henle can be varied to show
190 'the effects.
200 '
210 'This is a 'put and take' model, it takes
220 'the solute and puts it in another
230 'location.
240 '
250 'It then calculates the concentrations,
260 'makes them equal, if necessary, and then
270 'puts the right amount of water where it
280 'should go.
290 SWITCH%=PEEK(3)'this is the IOBYTE in CP/M
    system
300 PRINT CHR$(27)"E"'this clears the video
    screen
310 PRINT"SIMULATE THE COUNTER CURRENT
    MULTIPLIER IN THE KIDNEY"
320 PRINT:PRINT
325 REM if you wish to EXCLUDE a descending
326 REM pump then REMOVE the REM in line 327
327 REM LET P1=0' otherwise delete line 328
328 IF P1=0 THEN 360
330 INPUT "ENTER THE DESCENDING PUMP MULTIPLIER
    (0-460)",P$
340 IF VAL(P$)<0 OR VAL(P$)>460 THEN PRINT
    CHR$(7)"VALUE OUT OF RANGE!(0-460)":GOTO 330
350 P1=VAL(P$)
360 INPUT "ENTER THE ASCENDING PUMP MULTIPLIER
    ",P$
370 IF VAL(P$)<0 OR VAL(P$)+P1>460 THEN PRINT
    CHR$(7)"VALUE OUT OF RANGE!(0-460 TOTAL ALL
    PUMPS)":GOTO 360
380 P2=VAL(P$)
390 INPUT"ENTER THE INTERSTITIAL WASHOUT RATE
    (0-1) ",P$
400 IF VAL(P$)>1 THEN PRINT CHR$(7):GOTO 390
410 WASH=VAL(P$)
420 INPUT"ENTER LENGTH OF THE LOOP OF HENLE (5-
    15) ",P$
430 IF LEN(P$)=0 THEN L=10:GOTO 460
440 IF VAL(P$)<5 OR VAL(P$)>15 THEN PRINT
    CHR$(7):GOTO 420
450 L=VAL(P$)
460 DIM QDHL(L),QINS(L),QAHL(L),VDHL(L),VAHL(L),
    DHL(L),CINS(L),CAHL(L),VINS(L)
470 FOR I=0 TO L'SET UP INITIAL VALUES
480 DHL(I)=300:CINS(I)=300:CAHL(I)=300
490 VDHL(I)=24:VAHL(I)=24:VINS(I)=24
500 QDHL(I)=DHL(I)*VDHL(I)
510 QAHL(I)=CAHL(I)*VAHL(I)
520 QINS(I)=CINS(I)*VINS(I)
530 NEXT
540 PRINT CHR$(27)"E"'clear the screen
550 GOTO 940
560 PRINT CHR$(27)"E"'clear the screen
570 PRINT CHR$(27)"H";'this command puts the
    cursor in the upper left corner of screen
580 IF P$="P" THEN POKE 3,SWITCH%+2:P$=""'turns
    on the printer
590 PRINT TAB(7)"CONC DHL";
600 PRINT TAB(19)"VOL DHL";
610 PRINT TAB(30)"CONC INS";
620 PRINT TAB(43)"CONC AHL";
630 PRINT TAB(52)"VOL AHL"
640 VDHL(0)=24:DHL(0)=300:
    QDHL(0)=DHL(0)*VDHL(0)'glomerular filtrate
650 FOR I=0 TO L-1'NOW FIND THE NEW STEADY STATE
660 QDHL(I)=QDHL(I)-1*P1:QDHL(I+1)=QDHL(I)'PUMP
    AND MOVE ON, TRANSFER TO NEXT
670 QINS(I)=QINS(I)+1*P2:QINS(I+1)=QINS(I)'PUMP
    AND MOVE ON
680 NEXT
690 FOR I=L-1 TO 0 STEP -1'shift solute and
    volumes from DHL to AHL
700 QAHL(I)=QDHL(L):VAHL(I)=VDHL(L)
710 NEXT
720 FOR I=L-1 TO 0 STEP -1'shift solute from 1
    stage to next
730 QAHL(I)=QAHL(I)-1*P2
740 QINS(I)=QINS(I)+1*P2
750 IF I>0 THEN QAHL(I-1)=QAHL(I)'PASSING
    THROUGH
760 NEXT
770 FOR I=0 TO L-1'calculate concentrations and
    shift fluids to match
780 V=(VDHL(I)*QINS(I)-
    QDHL(I)*VINS(I))/(QDHL(1)+QINS(I))'REDISTRIBUTION
    OF VOLUME
790 VDHL(I)=VDHL(I)-V'IN THE DESCENDING LOOP OF
    HENLE'
800 VINS(I)=VINS(I)+V'FROM TUBULE TO
    INTERSTITIUM TRANSFER
810 VDHL(I+1)=VDHL(I)'MOVE IT ON DOWN
820 CAHL(I)=QAHL(I)/VAHL(I)'NOW CALCULATE NEW
    CONCENTRATIONS
830 DHL(I)=QDHL(I)/VDHL(I)
840 CINS(I)=QINS(I)/VINS(I)
850 NEXT
860 FOR I=0 TO L-1
870 VAHL(I)=VDHL(L-1)
880 NEXT
890 FOR I=0 TO L
900 VINS(I)=24
910 Q=WASH*QINS(I)-300*24:IF Q<0 THEN Q=0
920 QINS(I)=QINS(I)-Q
930 NEXT
940 FOR I=0 TO L-1'display the results of this
    round
950 PRINT USING "##";I;
960 PRINT TAB(5);
970 PRINT USING "XX ###.##";DHL(I);
980 PRINT USING "   ###.##";VDHL(I);
990 PRINT USING " XX    ###.##";CINS(I);
1000 PRINT USING "     XX ###.##";CAHL(I);
1010 PRINT USING "###.##";VAHL(I);
1020 PRINT " XX"
1030 NEXT
1040 PRINT TAB(5)"X";
1050 PRINT TAB(6)STRING$(52,"X");
1060 PRINT TAB(58)"X";
1070 PRINT
1080 PRINT"The higher numbers move down into the
     medulla"
1090 PRINT"Watch for stability in the values for
     the new steady state"
1100 PRINT"Present Pump Multiplier Values are:"
1110 PRINT "Washout rate =";WASH;
1115 IF P1=0 THEN 1130
1120 PRINT TAB(40)"Descending Pump =";P1
1130 PRINT TAB(40)"Ascending  Pump =";P2
1140 PRINT" Depress the space bar - to stop the
     program - restart with RUN"
1150 DHL(0)=300:VDHL(0)=24:
     QDHL(0)=VDHL(0)*DHL(0)
1160 POKE 3,SWITCH%
1170 P$=INKEY$:IF P$=" " THEN END
1180 GOTO 570
```

The washout rates are given in the assignment = WASH. It is a relative rate from 0 to 1. The amount of washout of solutes in the interstitium is calculated as Q = WASH*QINS(I) − 300*24 and QINS(I) = QINS(I) − Q. The rate of washout is therefore proportional to the amount that is there, and it should behave as a passive diffusion process. If Q becomes greater than what there is; it is assigned a value of zero.

SWITCH% = PEEK(3) is the content of memory location (3), in a CP/M system this defines the output device. Adding 2 to this location will turn on the printing device that is currently configured. In this program typing a "P" will result in a printed display.

Method of Presentation

The program is designed to be operated by students as the background to a laboratory-workshop that involves the quantitative concepts of renal physiology. Several

microprocessors are available to be used on an informal basis by groups of several students during this pencil and paper laboratory exercise. The students can experiment with the various parameters as they apply to a counter-current multiplier system. This is not an attempt to represent how various drugs work by decreasing the rate of pumping, that teaching task belongs to pharmacologists. This model is intended to demonstrate countercurrent multiplication as a simple physical principle.

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Letter to the Editor

Organismal Mapping

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Joseph Engelberg's pleas (1) for more consistency and rigorousness in drawing "organismal maps" is most welcome. Nevertheless, I suggest that Figure 2 of his article itself contains a possible source of confusion. In that diagram, a primary disturbance or perturbation in the cycle, namely a sudden increase in plasma Ca^{2+} level, is shown as causing a decrease in parathyroid hormone (PTH) secretion rate. However, two different methods are used in the one diagram to indicate the negative or inhibitory nature of this effect: *1*) the broken-line connecting arrow as used by Riggs and *2*) the small arrow (↓) (following the ↑ to the left of "plasma Ca^{2+} conc"). In this instance there is no real difficulty, since Figure 2 is clearly intended only as explanation of part of Figure 1; but taken in isolation, this part of Figure 2 might be misread as "an increase in plasma Ca^{2+} inhibits the decrease in PTH secretion rate." In general it is better not to use the two conventions in one and the same diagram. The "↑, ↓" convention is particularly useful if it is wished to stress (in a composite diagram or a pair of related ones) the different mechanisms of response to opposite primary perturbations, for example, an increase in plasma Ca^{2+} affecting predominantly the secretion of calcitonin, a decrease affecting that of PTH.

In an earlier issue of *The Physiologist* (2), mention was made of a monograph by C. Allweis, published as a supplement to *Israel Journal of Medical Sciences* but unfortunately not distributed with that journal (3). In that monograph the great confusion existing among published physiological control-system diagrams was examined, and a new convention was proposed. Some features of this proposal were summarized in a short paper of my own (4), and it has been adopted in one British textbook (5). A more recent presentation was given by Allweis at the 29th International Congress of Physiological Sciences (6). In Allweis's proposal a broken-line arrow represents a cause-and-effect relationship mediated by a nerve connection no matter whether the effect is stimulation or inhibition and thus has a different meaning from Riggs' usage of the same symbol.

These possible sources of confusion are among the matters that might well be examined in the search for "some common convenient scheme" as urged by Engelberg (1).

References

1. Engelberg, J. Integrative physiology: on mapping the organism. *Physiologist* 26: 142–144, 1983.
2. *Physiologist* 15: 36, 1972.
3. Copies of the monograph can be obtained from the US National Technical Information Service or (in the UK) from Microinfo Ltd., PO Box 3, Alton, Hampshire GU34 1EF. Purchasers should enquire of the appropriate supplier about availability and the price, which is now much greater than quoted in Refs. 2 and 4.
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Correction

Physiologist 26(6): Suppl., 1983. Arnauld Nicogossian, Sam L. Pool, and Paul C. Rambaut. "Cardiovascular Responses to Spaceflight." Pages S–79: column 2, paragraph 1, line 29 should read: hypovolemia or dehydration.

Preface

The author has always been fascinated by accounts of the electrical treatments applied by physicians in the golden era of electrotherapy which extended from the late 1700's to the early 1900's. He has also been fascinated by the ingenious electromechanical devices that physiologists developed to stimulate irritable tissue. It is hoped that, while reading this monograph, the reader will share this fascination; for this was the reason for composing the monograph.

During the golden era of medical electricity, physiologists were preoccupied with understanding the process of excitation using the frog nerve-muscle preparation. Surprisingly, the basic science discoveries were slow to be applied to an understanding of the electrotherapeutic techniques. Therefore, in their quest for new therapies, clinicians usually applied electric current to the body with little regard for potential hazards. Often the electrotherapies were without adequate rationale, even though considerable benefit was derived from some of them. However, there was some quackery associated with medical electricity; but this subject will not be dealt with here.

The monograph deals with two aspects of the application of electric current to living tissue: 1) stimulators and the basic-science research that led to discovery of the law of excitation, and 2) the various uses of electric current to alter function as applied by the clinician. Wherever possible, the author has provided the logic and rationale offered by the various investigators. Also, wherever possible, quantitative data are provided. The potential value of discarded techniques is pointed out where appropriate.

The monograph begins with the static electricity machine and the Leyden-jar (capacitor). Examples of the therapeutic applications of their use, called Franklinic electricity, are presented. Discovery of the electrochemical cell by Galvani and Volta, and the type of stimulus it provides follows, being complemented by therapeutic applications (galvanotherapy). The evolution of the induction coil (faradic) stimulator is traced and the two types of stimuli it produces are described. Faradic electrotherapy is discussed extensively . The effect of high-frequency current on living tissue is presented, along with its therapeutic applications in the form of diathermy and electrosurgery.

The monograph concludes with a chapter that outlines discovery of the law of excitation which relates the intensity and duration of a stimulus. Expounded separately by Weiss and Lapicque, the law is examined in view of our present knowledge of excitation based on the membrane theory. Using the latter, the strength-duration curve is derived analytically. Finally, the two strength-duration curves are compared, revealing that the empirically derived curve is not very different from that having a sound theoretical basis.

This monograph was made possible by the contributions of many. The author wishes to thank The Minneapolis Foundation, which through the University of Minnesota's (U of M) Program in the History of Science and Technology, provided fellowship support for this research during two months in the summer of 1982.

The author wishes to thank Earl Bakken, and the personnel at the Bakken Library of Electricity in Life (BLEL), in Minneapolis for the opportunity to make this site headquarters for the study. Nancy Roth, Dorina Morawetz, Elizabeth Ihrig, Mike Welch and Albert Kuhfeld, all of the BLEL were always ready to help the author find rare manuscripts, journals and books. The library resources provided by the U of M, particularly those of the Wangensteen Collection, made it possible for the author to obtain original basic science and clinical journals. The peace and serenity of the BLEL, along with its impressive collection of rare ɔks, provided the author with a rewarding, stimulating and therapeutic experience.

Finally, the author wishes to acknowledge the contributions of Kim Gilbert and Chris Ramsey for their help in doing all the important, but often un-noticed things that were needed to create this monograph.

L.A. Geddes
December 31, 1982

Contents

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Chapter 1. Physics, Physiology and Electrotherapy

Discoveries in physics led physiologists to create stimulators which were applied immediately by physicians to treat a remarkable variety of afflictions. While physicists concerned themselves with the laws that governed the flow of "electric fluid", the name used for current, physiologists sought to discover how current excited living tissue. The history of electric stimulation is thus linked inextricably with discoveries in physics. However, the therapeutic applications of electric current ran well ahead of the necessary knowledge of the electrophysiology of excitation. The following chapters describe the events that led to discovery of the law of excitation and the therapeutic application of four types of current: static or franklinic electricity (including capacitor discharge), direct or galvanic current, induction - coil or faradic current and high - frequency or d'Arsonval current. This chapter will highlight some of the studies with each type of current.

Discovery that electricity could stimulate excitable tissue, such as nerve, muscle and sensory receptors was a remarkable event that had its origin in antiquity. Probably the earliest experiences were of the considerable shocks delivered by electric fish, accounts of which date from 2750 BC. (Kellaway 1946). Static electricity was discovered by Thales around 400 BC, when he rubbed amber and obtained the amber, or using the Greek, electric effect. Development of the capacitor around 1745 permitted the accumulation of considerable charge and consequently the delivery of a very strong shock, the nature of which had to await the interest of W. Thomson (Kelvin) who was concerned with the capacitance of submarine telegraph cables and the role that capacitance played in limiting signaling rate.(1853)

The experiments of Sulzer (1753, 67) and Gavalni (1791) led Volta (1800) to discover direct current. The law that governed its intensity was presented by Ohm (1827) who introduced the concept of resistance.

The discovery of electromagnetic induction by Faraday and Henry in 1831 led DuBois - Reymond (1848) to create the induction - coil (inductorium) stimulator which, for a long time, was the central tool for physiological investigation. Unlike the capacitor discharge, which produced a single stimulus, and unlike direct (galvanic) current, which only produced a response when the current was initiated and arrested, the induction coil produced a train of stimuli that could tetanize skeletal muscle. More importantly, it allowed stimulation of autonomic nerves, which almost immediately revealed a new phenomenon: inhibition.

At the dawn of the twentieth century, a modified induction coil in the hands of d'Arsonval, physicist and physician, permitted the generation of high-frequency alternating current. To the surprise of all, this type of current did not stimulate, but it did heat excitable tissue.

From the examples just given. There arose a considerable interest in discovering the fundamental properties of a stimulus. Although capacitor discharges were used widely by lay persons for entertainment, physiologists were slow to adopt them because the nature of the capacitor discharge current waveform was unknown until 1853 when Thomson (Kelvin) solved the first-order differential equation that describes the exponential nature of current in the resistance-capacitance circuit. By the 1890's it was common knowledge that the capacitor-discharge waveform was exponential. Louis Lapicque, with his wife in 1909, became the champion of capacitor-discharge stimulation.

In 1848, Du Bois Reymond stated emphatically that direct (galvanic) current exerts its stimulating effect only at the make and break of the current flow. However, Pfluger (1859) showed that a continuous current also produced a physiological response. Under the cathode, excitability was increased and under the anode, excitability was decreased. Thus was discovered the phenomenon of electrotonus.

In the latter part of the nineteenth century, it was realized that stimuli from the capacitor and induction-coil were difficult to quantitate. There thus arose an interest in creating single rectangular pulses of current in which the intensity and duration could be varied independently. To meet this requirement, mechanically operated contact systems were developed; usually a first pair of contacts constituted a short circuit across the stimulating electrodes; the second pair of contacts was in series with the voltage source. When the first pair of contacts was opened, the stimulating current started to flow and was arrested milliseconds later when the second pair opened. Such devices were known as rheotomes, or current slicers.

The controversy between Edison and Tesla over the best type of electric current for commercial sale was the event that stimulated physiologists to examine the stimulating properties of sinusoidal alternating current of increasing frequency. The issue of the relative danger of alternating versus direct current was addressed by d'Arsonval, who, at the turn of the twentieth century, showed that as the frequency was increased, the stimulating ability decreased. When a frequency in excess of 100,000 cycles per second (Hz) was reached, excitable tissue could not be stimulated, even with high-intensity current; however, it was warmed.

Unfortunately the extensive physiological studies did nothing to settle the controversy over the selection of direct or alternating current for commercial

sale; although the research led directly to the creation of diathermy and electrosurgery. The controversy was settled by recognition of the higher efficiency and improved flexibility associated with long-distance transmission of alternating current.

The beginnings of electrotherapy date from Ramsden's introduction of the rotating-disk static-electricity machine around 1768. Immediately physicians began to use it to electrify patients to treat a wide variety of afflictions. Static-electricity machines were also used to charge Leyden jars which were then discharged through the limbs of patients with different forms of paralysis. Not surprisingly, many hysterical paralyses were "cured".

Just after Volta described his battery in 1800, physicians applied "galvanic" current to the body to treat many diseases. The refreshing, relaxing and analgesic effect of galvanic current was widely acclaimed; although the reported "cures" were difficult to verify. The discovery by Humphry Davy (1807) that galvanic current could extract metallic ions from the body led to the electric bath in which the patient lay while current flowed through the water. It appears that the physicians believed that poisons and disease could also be extracted by the galvanic current.

The surgical problem of the late 1900's related to complications arising from chloroform anesthesia. Cardiac and respiratory arrest were not uncommon. The galvanic battery saw considerable service in emergency resuscitation. Typically the diaphragm was twitched by intermittent phrenic - nerve stimulation, effected by applying a battery of 200 cells (about 300 volts) to an electrode on the neck and one on the left side of the chest at about the seventh pair of ribs. A strong twitch of the respiratory muscles ensued and a strong inspiratory effort occurred. It is likely that the ventricles were stimulated each time the current was applied. Not surprisingly there were many successful resuscitations.

The medical applications of faradic current are too numerous to summarize here. Not only were sensory nerves stimulated, but motor and autonomic nerves were also targets for the current. The "electric-hand" treatment placed the physician in series with inductorium and the patient. The physician's hand constituted the exploring electrode which was passed over the body; Duchenne (1872) pioneered use of this technique. Faradism, like galvanism, was applied indiscriminately. There were, however, some sudden deaths associated with faradism - probably due to ventricular fibrillation. For example, respiratory arrest due to chloroform was often treated by stimulating the phrenic nerve via neck and left - chest electrodes. Each time the current was applied, a strong tetanic contraction occurred in the diaphragm, resulting in a strong inspiratory effort. Although successful resuscitation was common, a sudden loss of the pulse was occasionally reported, probably due to ventricular fibrillation.

Physicians immediately took advantage of the inability of high-frequency current to stimulate and created two new medically valuable techniques: diathermy and electrosurgery. In the former, tissue heating was produced by applying two large-area conducting electrodes to the skin and delivering about one ampere of high-frequency current. Nagelschmidt (1907, 28) became the pioneer in this technique. Later, capacitive electrodes were used and inductive coupling soon became popular. In the latter case, the body, or part of it, was placed in a coil carrying the high-frequency current. The relaxing, analgesic and vasodilating effect of diathermy is still of value in medicine.

At the dawn of the twentieth century Doyen (1909) in France and Clark (1911) in the USA sought a different application for the non-stimulating properties of high-frequency alternating current. They found that when such current was passed into living tissue via a point electrode, dessication, coagulation and cutting could be produced, the effect being related to the current intensity. From these studies, electrosurgery was born. Popularization of electrosurgery is due to Harvey Cushing who, in 1928, demonstrated its superiority to the scalpel for neurosurgery.

Detailed accounts of the events just described appear in the various chapters of this monograph. Emphasis has been placed on identifying those who contributed important information toward defining the essential requirements of a stimulus. The medical applications are presented in view of present - day knowledge of stimulation and may indicate that some discarded techniques may merit re-investigation.

Chapter 2. Static Electricity and Capacitor Stimulators, Including Therapeutic Applications

Stimulators

That electricity could be created by rubbing amber was known to the Greeks. In fact the Greek name for amber is elektron, the name became used to describe the amber effect. When rubbed, other substances exhibited the electric effect by their ability to attract particles of pith and scraps of parchment. There soon developed a constant striving to create more efficient generators of electricity. According to Mottellay (1975), Von Guericke developed the rotating sulfur-ball generator around 1660; but the first practical device was due to Ramsden who introduced the rotating glass-disc machine in 1768 (Figure 2-1A), which was ideally suited to charging the Leyden jar (capacitor) that appeared in 1745. Originally the Leyden jar (Figure 2-1B) consisted of a phial filled with water into which an electrode dipped. The other conductor consisted of the hand of the subject holding it. Discovery of the Leyden jar is usually accorded to Van Musschenbroek and Von Kleist in 1745. According to Burnham (1963), later models (Figure 2-1C) consisted of tin foil on both sides of a glass phial; this version was introduced by John Bevis in 1746. Almost immediately the Leyden jar was put to use as a stimulator for entertainment purposes. A favorite diversion involved arranging subjects in a semi-circle and having them join hands. Then a charged Leyden jar was connected to the free hand of the first and last subject. Immediately they all jumped, providing great entertainment for the spectators.

So attractive was the medical potential of the Leyden jar, that according to Heilborn (1979), in 1752 the number of medical publications devoted to it (40) was almost equal to those published on all other aspects of its use (55). By 1789 the number describing medical applications had risen to 70, with only 30 devoted to the physical aspects of electricity.

The charged Leyden jar provided a potent, but not quantifiable stimulus. Before it could be used as an investigative tool, the concepts of charge, its movement (which is current), potential difference (the force that moves charge), capacitance and the temporal nature of current flow from a capacitor had to be understood. The concept of electric charge was due to Coulomb (1785) who measured the force between charged bodies. From his studies there evolved the foil-leaf electroscope, the separation of the leaves being proportional to the potential. The concept of potential (or tension) also emerged from use of the voltaic pile. An understanding of current flow and potential arose from the studies of Ohm (1827) who investigated the conducting properties of metal wires. However a

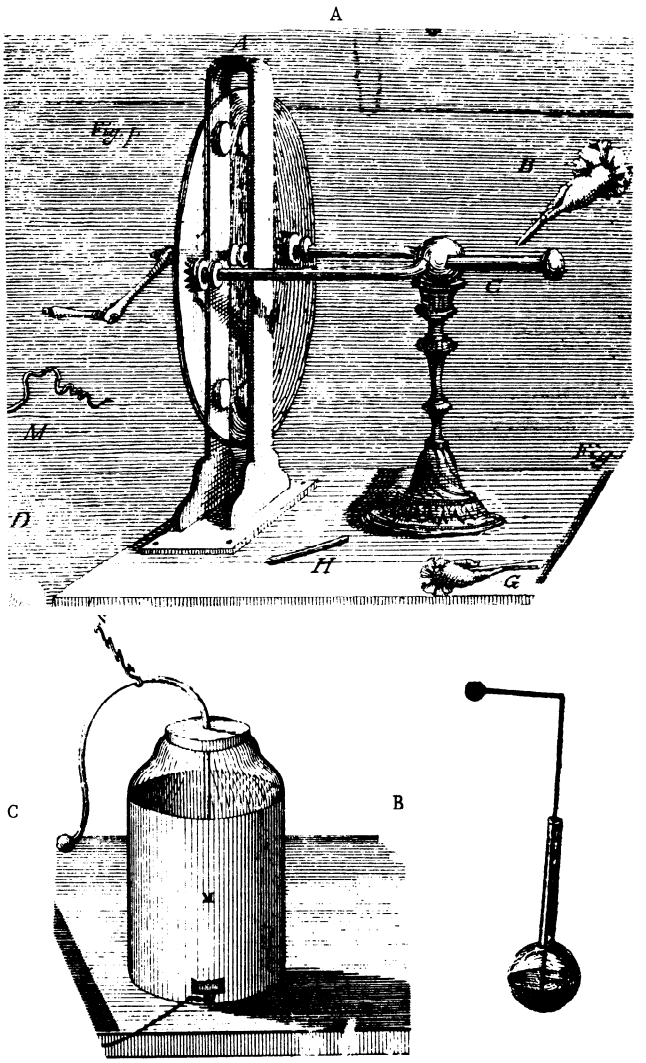


Figure 2-1. Static electricity stimulators. A illustrates the Ramsden generator used by Galvani (DeViribrus 1791). B illustrates one of the earliest Leyden jars (Kruger 1746) and C illustrates the traditional Leyden jar which appeared before the turn of the 18th century; the model illustrated was used by Wheatstone (1843).

knowledge of the nature of the discharge of the Leyden jar evolved slowly. In the early 1800's there were no galvanometers or rapidly responding indicators of current. These devices did not appear until the late 1800's. Accordingly there was no instrument capable of displaying the temporal nature of the capacitor-discharge current. Wollaston (1801) discharged a Leyden jar via two electrodes placed in acidulated water and analyzed the composition of the gas at each electrode. He wrote, "I observed that each wire (electrode) gave both hydrogen and oxygen gas, instead of that being formed separately by the electric (voltaic) pile." Thus the first experiment on the nature of the capacitor discharge provided information that is contrary to fact. Wollaston's results indicated that the discharge was oscillatory, an event that

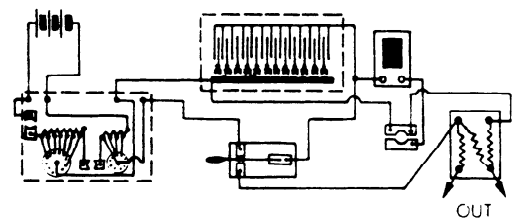
we now know could occur only if there were inductance in the discharge circuit. The matter was resolved by Thomson, Lord Kelvin, (1853) who was investigating the factors that limit the rate of telegraphic signalling over submarine cables. He showed mathematically that the current waveform for a capacitor discharge is exponential, and the duration of the current pulse is proportional to the product of the capacitance and the resistance through which the current flows.

It is difficult to ascertain who first used the capacitor-discharge to stimulate excitable tissue. d'Arsonval (1881) pointed out that the strength of an induction-coil shock was difficult to quantitate and proposed that a capacitor charged to a known potential, could serve as a quantitative stimulus. A few years earlier, Tiegel (1877) presented a study comparing capacitor-discharges to induction-coil shocks. However it was Hoorweg (1892) who conducted the first quantitative studies with capacitor-discharge shocks; but it was Lapicque (1905,09) who popularized their use and developed the strength-duration curve which describes the requirements for stimulating excitable tissue with different duration pulses.

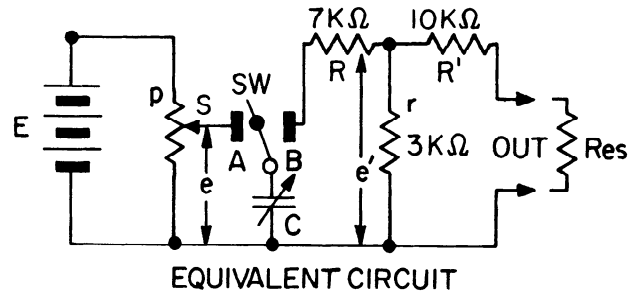
Two events made the capacitor a quantitative stimulator: 1, development of the electrochemical cell by Volta (1800), and 2, development of the potentiometer by Wheatstone (1843). Before introduction of the potentiometer, the stimulus strength (i.e. capacitor voltage), could only exist as a multiple of cells, i.e. 1D, 2D, 3D, etc., D referring to the Daniell cell; other letters were used to identify other cells such as Bunsen, Grove or Leclanché, etc. With the slide-wire potentiometer, a capacitor could be charged to any value from 0 to the voltage corresponding to a battery of any number of cells connected in series. Thus, fine control over the intensity of a stimulus became possible.

A typical capacitive stimulator of the day, developed by Lapicque, is shown in Figure 2-2. The capacitor C was charged to e, which could be any fraction of the voltage E of the battery, depending on the position of the slider (S) on the potentiometer (P). The capacitor was then discharged by moving the switch (SW) from A to B. The duration of the discharge current was made relatively insensitive to the variable (and unknown) resistance of the electrode-subject circuit (Res) by three resistors: R, r and R'. Resistor R' was made high with respect to the assumed resistance (Res) of the electrode-subject circuit. In this way, any variation in resistance of the electrode-subject circuit would not appreciably alter the delivered current which resulted from e', the voltage across r.

The resistance r was made low with respect to R'+Res. Therefore, variations in R'+Res would not appreciably alter r. The time constant of discharge was therefore equal to (R+r)C. Thus a capacitor



LAPICQUE CHRONAXIE APPARATUS



EQUIVALENT CIRCUIT

Figure 2-2. A typical capacitive stimulator. A illustrates the Lapicque stimulator and B is the equivalent circuit (Courtesy Grass Instrument Co., Quincy, MA).

value C could be selected, charged to e volts and discharged through R+r. The stimulating current was very close to e'/R', where e' equals er/(r+R). In this way, it was possible to determine the current intensity versus stimulus-duration (time constant = RC) relationship for an excitable tissue. This was the type of stimulator used by Lapicque to determine the current strength-duration curves for a variety of excitable tissues

Therapeutic Applications

In the therapeutic applications, a capacitor was usually charged to a high voltage by a static-electricity machine. The subject was part of the discharge circuit. Usually a spark accompanied the discharge.

Static electricity was applied in two ways: to the whole body on an insulating support, or via a local electrode from which a spark was drawn. In another localized application, a capacitor discharge was used. When sparks occurred, the voltage was high and the current was low in intensity. The spark discharge current was a single pulse of exponentially decreasing current. However if there were some inductance in the circuit the discharge could be oscillatory and consist of a damped sine wave. Thus a single short-duration pulse or a few short-duration pulses of alternating current could have been delivered.

A capacitor discharge pulse can stimulate a motor nerve and skeletal muscle to produce a twitch. Sensory nerves and receptors can also be stimulated, giving rise to a sensation resembling a strong pin prick. If intense enough, a static discharge can evoke an ectopic beat

in the heart. Under special conditions,(e.g. myocardial infarction) ventricular fibrillation can be induced. This latter event was apparently rare, for deaths from electrostatic discharge were virtually unknown. With these physiological responses in mind, the therapeutic uses for static discharges will now be reviewed.

The use of static electricity took three forms: electrification of the whole body, drawing sparks from the body and discharge of the Leyden jar through electrodes placed over specific regions. The term electric air bath was used to describe the first method, sparking or electric wind designated the second and localized discharge identified the third method. An excellent historical review of therapy with static electricity was presented by Althaus (1873) who stated that static electrotherapy began in 1744. Two authoritative textbooks on static electricity were published by Cavallo in 1780 and 1786. Detailed recommendations were presented for the treatment of a variety of ailments. By 1841 an electrical therapy room had been developed at Guy's hospital in London by Bird, for the treatment of a variety of diseases using the three methods just identified. Bird wrote: "A competent female attendant resides in the apartments attached to the room for the purpose of keeping the apparatus in order, and applying electricity to the female patients. In this manner, every case is registered; its progress watched by the pupils and any change of treatment is directed by myself." His paper tabulates the successful treatment of a very large number of diseases.

Benjamin Franklin pioneered the study of lightning and showed that it was the same as electricity derived from static-electricity generators. However it is surprising that Franklin's name became associated with the therapy, because it had been practiced in Italy and Germany before Franklin used it on paralytics; this fact is stated clearly in Franklin's account (1769) of his experiences related in a letter to John Pringle, M.D., dated December 21, 1757. The letter reads in part,

"Some years since, when the newspapers made mention of great cures performed in Italy and Germany, by means of electricity, a number of paralytics were brought to me from different parts of Pennsylvania, and the neighboring provinces, to be electrified, which I did for them at their request. My method was, to place the patient first in a chair on the electric stool, and draw a number of large strong sparks from all parts of the affected limb or side. Then I fully charged two six gallon glass jars, each of which had about three square feet of surface coated; and I sent the united shock of these through the affected limb or limbs, repeating the stroke commonly three times each day. The first thing observed, was an immediate greater sensible warmth in the lame limbs that had received the stroke, than in the other; and the next morning the patient usually related, that they had in the night felt a pricking sensation in the flesh of the paralytic limb; and would sometimes show a number of small red spots, which they supposed occasioned by those prickings. The limbs, too, were found more capable of voluntary motion, and seemed to receive strength. A man for instance, who could not the first day lift the lame hand off his knee, would the next day raise it four or five inches, the third day higher; and on the fifth day was able, but with a feeble languid motion, to take off his hat. These appearances gave great spirits to the patients, and made them hope a perfect cure; but I do not remember that I ever saw any amendment after the fifth day; which the patient perceiving, and finding the shocks pretty severe, they became discouraged, went home, and in a short time relapsed so that I never knew any advantage from electricity in palsies that was permanent. And how far the apparent temporary advantage might arise from the exercise in the patient's journey, and the coming daily to my house, or from the spirits given by the hope of success, enabling them to exert more strength in moving their limbs, I will not pretend to say.

"Perhaps some permanent advantage might have been attained, if the electric shocks had been accompanied with proper medicine, a regimen under the direction of a skillful physician. It may be, too, that a few great strokes as given in my method, may not be so proper as many small ones; since, by the account from Scotland, of a case, in which 200 shocks from a phial were given daily, it seems that a perfect cure has been made. As to any uncommon strength supposed to be in the machine used in that case, I imagine it could have no share in the affect produced; since the strength of the shock from charged glass, is in proportion to the quantity of surface of the glass coated; so that my shocks from those large jars could have been much greater than any that could be perceived from a phial held in the hand.

"I am, with great respect,
Sir,

"Your most obedient servant, B.F."

It is clear that Franklin used the second and third methods of electrotherapy. It is equally clear that Franklin did not claim that therapy with static electricity was a cure for all types of paralysis.

The Electric Air Bath

Electrification of the whole body using the electric air bath was perhaps the most spectacular of the static-electricity therapies. The patient was usually seated on a stool on a well insulated platform (about 27"X42"), the legs of which were about 10 inches high and of glass. One electrode from the static-electricity machine was connected to

ground and the other was fastened to the patient's clothing, or held in the hand (Figure 2-3). The static-electricity machines used were quite impressive; although a single-disk unit was used in the early days, instruments with six 24" glass disks were not uncommon in the heyday of franklinism. The polarity chosen depended upon the desired effect. With the patient connected to the positive terminal, exhilaration was obtained; but with the opposite polarity a feeling of prostration was encountered. Obviously the positive electric air bath was used most frequently.

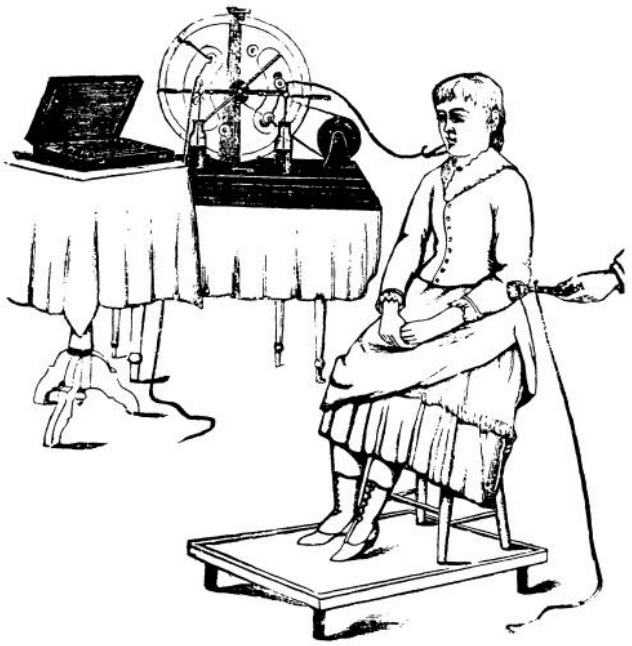


Figure 2-3. The electric air bath consisted of electrifying a patient seated on a stool which was on an insulating platform supported by short glass legs. One conductor of the static electricity machine was connected to the patient's clothing (or held in the hand), the other was connected to ground. The therapist's hand holding grounded electrode over the subject's elbow illustrates the method for drawing sparks. From Electrotherapeutics, Haynes, C. M., Chicago 1896. 507pp.

The response to the positive air bath was certainly dramatic. When the static-electricity machine was activated adequately, the patient's hair on the head and exposed surfaces rose. If the patient was in the dark, a halo (corona discharge) surrounded the body. The patient felt warm, exhilarated but relaxed and perspired slightly. The face was usually flushed and the pulse rate increased. Often the patient felt drowsy and desired to sleep after the treatment, which lasted about 15-30 minutes; however, periods up to three hours were occasionally used.

The therapeutic indications for the electric air bath were many; perhaps the best was given by Garratt (1860) who wrote, "The author has found it of very marked advantage for some individuals who, after great sickness or calamity, remained in a low state of health, and yet present no discoverable reason why they should not get better, only that there is a low tone of the nerves and functions, that cannot be reached by medicine or regimen." Other indications for use of the electric air bath were many of the symptoms of hysteria, paralysis, aphonia, hemianesthesia, catalepsy, contractures and obstinate pain, particularly from rheumatism. It was also recommended as a treatment for chorea and torticollis.

The negative air bath (i.e. patient negative) was recommended by Althaus (1873) for erysipelas, chronic inflammation, headache and neuralgia. However he pointed out that the physiological effects with this modality were inconsistent. It is somewhat surprising that Althaus, an apparent believer in the electric air bath wrote, "It is said that during the discharge, heat is evolved, circulation quickened, and the secretions, especially perspiration, become active; but it is very doubtful whether these are constant physiological effects of the bath; probably they are merely caused by the excited imagination of the patient."

Drawing Sparks

Drawing sparks from the electrified body in the air bath was accomplished with several different types of metal electrode: a ball (1-3 inches in diameter), a point, a brush or a roller. With all, the clothing did not have to be removed, (a desirable attribute in the prim Victorian era). The sparks were usually drawn from the back over the spinal column. Each electrode was mounted on an insulating handle and when used, the electrode was connected to ground. As the electrode was brought near the subject, a spark was struck. The ball produced a series of discrete localized sparks in rapid succession. The pointed electrode produced a brush or spray discharge when close to the skin. The roller often had small projections so that, as it was rolled over the clothing on the back, the sparks were struck from the points.

The type of sensation experienced by the patient depended on the length of the spark, which was a function of the distance of the electrode from the skin. Typical distances were from 1/4 inch to 1 inch. With the former, the sensation was of a pin prick; with the latter, the shocks were painful and produced muscle twitches. The spark usually produced a red spot with a circumscribed white wheal. The response appeared in about five minutes and usually disappeared in a few hours. The indications for such shocks were hysterical paralysis, neuralgia, rheumatic pain, amenorrhea and other less obvious ailments.

Localized Capacitor Discharge

For the localized discharge, a charged Leyden jar (capacitor) was used. The discharge was usually delivered to the body by bringing the active electrode to the apparent site of the complaint. The other side of the Leyden jar was connected to another electrode on the subject or to ground. The discharge was usually intense. The indications for use were paralysis, pain (especially rheumatic) and amenorrhea.

Sparks were delivered to virtually every region of the body for the most amazing reasons, such as barrenness (infertility) in women and impotence in men. Figure 2-4 illustrates the drawing of sparks from the genitalia.

The response to localized discharges from the Leyden jar was painful and usually accompanied by a muscular twitch. This form of therapy saw much less used than the other two modalities.

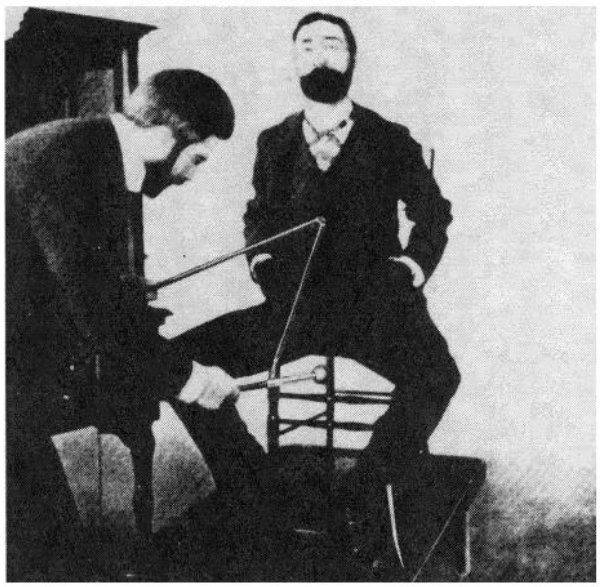


Figure 2-4. Drawing sparks from the genitalia.

Perspective

It is interesting to speculate on the successes associated with franklinic therapy; however it is difficult to be enthusiastic about some of the obviously inappropriate applications of static electricity. It is surprising that there was so much hysteria to be treated. Notwithstanding, the success in treating this group could not sustain this mode of therapy. Perhaps Duchenne (1872) put it best when he wrote, "This genre of electricity could not withstand the proof of time and it has been abandoned frequently by general physicians, after having, on their part, the object of a kind of infatuation." Although physicians slowly convinced themselves of the inability of static electricity to cure diseases, there is no doubt that the spectacular events surrounding electrostatic therapy, and the feeling of exhilaration experienced by many patients, did much to keep this therapy alive far beyond its time.

Chapter 3. Galvanic (Voltaic) Stimulators, Including Galvanotherapy

Galvanic (Voltaic) Cell

Discovery of the electrochemical battery, consisting of a series of cells, provided a new type of current. Unlike the Leyden jar (capacitor), which produced a pulse of current, the electrochemical voltaic cell provided a constant and seemingly inexhaustible flow of current. Physiologically this meant that a long duration stimulus was available for investigative purposes and therapy. The voltaic cell assumed even more importance in energizing the induction coil, which provided a train of short-duration, but high-intensity pulses.

Discovery of the electrochemical cell is accorded to Volta, 1800, who opposed Galvani's (1791, 92) views on animal electricity. The famous controversy, (see reviews by Fulton 1936, Dibner 1952, Green 1953, and Geddes and Hoff 1971), resulted in the crown of cups, (Figure 3-1A), and the voltaic pile (Figure 3-1B), both of which produced substantial current, easily demonstrable by the delivery of a strong electric shock, production of a spark when a short circuit was being placed across its terminals, and heat developed in the short-circuiting wire. Later, the strength was indicated by the galvanometer and the decomposition of an electrolyte; the latter technique was used to define the standard ampere.

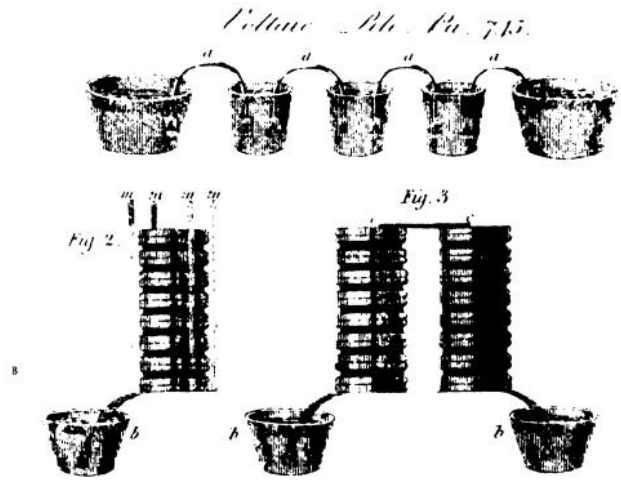


Figure 3-1. The first electrochemical batteries developed by Volta. Each cell consisted of a copper and zinc (couple) in an electrolyte. A illustrates the "crown of cups," a group of cells connected in series; B illustrates the Voltaic pile, in which the cells are stacked vertically, the electrolyte being contained in paper between each copper and zinc electrode. From Volta, Phil. (Trans. Roy Soc 1800, 90:403-431).

Although Volta's position is secure in the history of electricity, his discovery had been anticipated, but not explained, by Sulzer 1753,67) of Zurich, who conducted the interesting experiment sketched in Figure 3-2. He wrote (author's translation): "If one joins two pieces, one of lead and the other of silver in a manner that the two edges should make the same plane and that one brings them to the tongue, one will sense a certain taste, similar to the taste of vitriol of iron (iron sulfate); instead each piece alone gives not any trace of taste. It is not probable that by this junction of the two metals, there occurs a solution of one in the other, and the particles insinuate themselves in the tongue. It is then necessary to conclude that the junction of these metals effect one on the other, or on both, a vibration in their particles, and that this vibration, which must necessarily effect the nerves of the tongue and produce the taste sensation." Despite Sulzer's incorrect explanation for the taste, he had discovered the electrochemical cell, consisting of lead and silver, with saliva being the electrolyte.

Figure 3-2. The Sulzer experiment which anticipated Volta's discovery of the electrochemical cell. When dissimilar metals were in contact with the tongue, a bitter taste was perceived; either metal alone, or both metals unjoined and on the tongue produced no sensation. (Author's sketch).

Following Volta's introduction of the electrochemical cell, numerous investigators developed their own cells and arranged them in series to produce what became known as the "medical battery". The reason for the profusion of cells related to a desire to provide constancy and longevity of current flow. Table 3-1 presents a short compilation of the most popular cells of the nineteenth century. When arranged in series, the voltage (tension or electrical pressure) was equal to the sum of the voltage of each cell. Selection of the number of cells determined the strength of a stimulus until the potentiometer (rheocord) became available.

TABLE 3-1

VOLTAIC (GALVANIC) CELLS

INVESTIGATION AND YEAR	ELECTRODES AND ELECTROLYTES	POTENTIAL DIFFERENCE (VOLTS)*
VOLTA 1800	$Cu/H_2SO_4/Zn$ $Cu/HCl/Zn$	0.74-0.94
DANIELL 1836	$Pt/PtCl//ZnSO_4/Zn$	1.08-1.14
DANIELL	$Zn/ZnSO_4//CuSO_4/Cu$	1.058-1.16
GROVE	$Zn/H_2SO_4//HNO_3/Pt$	1.1-1.84
BUNSEN	$C/HNO_3//H_2SO_4/Zn$	1.96
LECLANCHÉ**	$Zn/NH_4Cl/MnO_2/C$	1.48

*Data from The Voltaic Cell. P. Benjamin, New York 1899. J. Wiley & Sons. 362pp. The voltage of a battery is the sum of the voltage of each cell. A typical cell, or couple of the late nineteenth century, provided a voltage of 0.74 to 1.96.

**This cell evolved into the so-called "dry cell" in which the NH_4Cl was contained in blotting paper. Such cells are widely used today.

Volta's copper and zinc cell (Figure 3-1) was the prototype for many that followed. Wollaston developed a very practical version in which the electrodes could be raised out of the electrolyte when not in use. Figure 3-3A illustrates his version of Volta's "crown of cups". Daniell improved Volta's cell by incorporating two electrolytes separated by a porous cup of unglazed porcelain; Figure 3-3B illustrates his cell. The Grove cell is illustrated in Figure 3-3C and the Bunsen cell is illustrated in Figure 3-3D. The Leclanché cell, which ultimately became the "dry cell" is shown in Figure 3-3E. To create the dry cell, the electrolyte was contained in blotting paper. Thus the "dry cell" is really a "damp cell".

Perhaps the most important galvanic stimulator for physiologists was that developed by Claude Bernard (1858) with which he discovered the action of curare. Figure 3-4 illustrates what he called the pincer stimulator which consisted of a voltaic pile of zinc and copper electrodes fashioned on two wooden arms connected together by a spring-metal member at the apex. The two points of the pincer constituted the stimulating electrodes. To activate the voltaic cells, Bernard soaked the assembly in vinegar.

In describing use of the pincer stimulator, Bernard wrote:

"It was for my experiments on curare and to show that this substance had the property that I discovered of destroying the nerve, but respecting the muscular irritability. But the little pincer, very adequate to excite the nerve since it needs a single arc of copper and zinc,

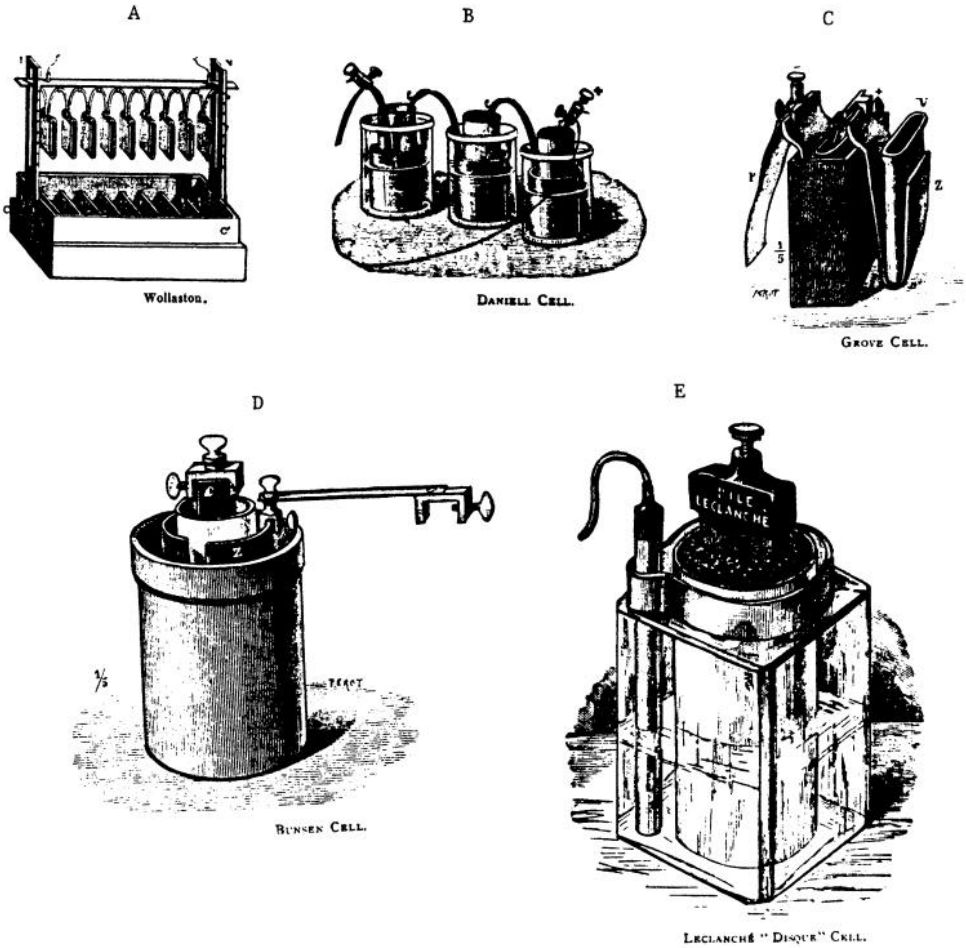


Figure 3-3. Various types of cells and batteries. Wollaston's version of the voltaic battery (A). Daniell (B), Grove (C), Bunsen (D), and Leclanché (E) cells.

demonstrated well that the nerve had lost its excitability; but it could not demonstrate that the muscle had retained its irritability, because it was not strong enough to excite a contraction by shaking it against the muscle itself.

"It was for this reason that I made a large electric pincer, in which the branches are made of many couples, which considerably augments the tension." Figure 3-4 illustrates Bernard's small and large pincer stimulators.

Galvanic or voltaic batteries were used to stimulate excitable tissue directly for investigative and therapeutic purposes, to charge Leyden jars, to operate the inductorium and to pass current through a heating element to create the electrocautery. Descriptions of these various application will be presented elsewhere in this monograph.

Therapeutic Applications

Introduction

Galvanic therapy involved passage of a constant electric current through the whole body (generalized therapy) or through a part of it (localized therapy). With generalized galvanism the positive electrode was placed on the head and the negative electrode on the epigastrum (or sacrum). An interesting form of generalized galvanism employed use of a tub of water in which the patient reclined. In localized galvanism, care was taken to specify the polarity, the current being described as descending or ascending; in the former case the positive electrode was central and in the latter it was distal to the neuraxis when peripheral nerves were treated.

The use of direct current evolved from Galvani's discovery (1791, 92) that a bimetallic couple touching the nerve and muscle of an isolated frog nerve-muscle preparation produced a twitch in the muscle. However it was Galvani's nephew, Aldini (1792, 1819), who popularized the stimulating effect of galvanic current. Interestingly enough, Aldini traveled to London to conduct experiments in which he applied a voltaic battery of 40 plates of zinc and copper in dilute muriatic (hydrochloric) acid, to electrodes at various sites on the body of a recently hanged criminal. The executed criminal had lain in a temperature of 30 deg F. for one hour and was then transported to the College of Surgeons. There, Aldini and several surgeons applied the conductors of the voltaic battery to different parts of the body and evoked strong muscular twitches.

Aldini (1819) gave the following account of one experiment that is particularly impressive.

"On applying the conductors to the ear and to the rectum, such violent muscular contractions were executed, as almost to give the appearance of the reanimination." Recall that these events occurred more than one hour after execution and certainly did much to attribute resuscitative powers to electricity.

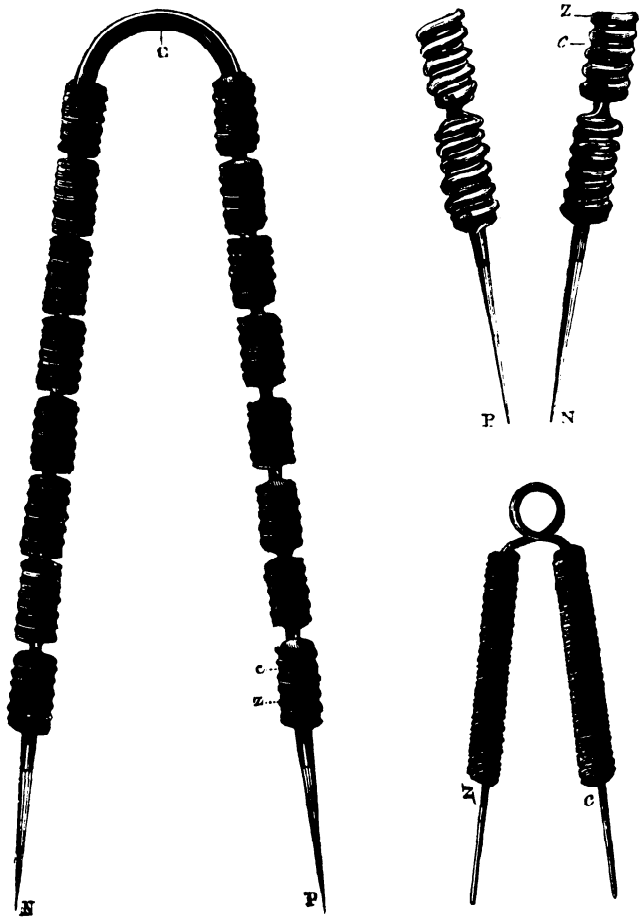


Figure 3-4. Bernard's electric-pincer stimulator. The smaller unit on the lower right was not adequately strong to twitch a muscle directly; although it could evoke a muscular contraction by nerve stimulation. To excite the muscle by direct stimulation, Bernard constructed the larger pincer stimulator (left) which consisted of zinc (Z) and copper (C) electrodes, the electrolyte used was vinegar. The pincer stimulator, was, in reality, two voltaic piles, one on each arm of the pincer. The voltage available from the larger pincer stimulator was about 16. (From Bernard C. Leçons Sur la Physiologie et la Pathologie du Systeme Nerveux. Paris, 1858. J-B. Balliere et Fils. Vol. 1, 520 pp (p. 144)).

The voltaic battery became the essential tool for galvanic therapy. By arranging a series circuit of voltaic cells, it became possible to send current of adequate strength through body-surface electrodes and obtain a physiological effect. Ironically Aldini used the voltaic battery which made galvanism possible. Associated with this, as with every therapy, there are the names of pioneers. The numerous textbooks on electrotherapy of the nineteenth century all identified Remak of Berlin as the father of galvanotherapy, although LaBeaume (1826) had published an interesting English-language text on the use of galvanism for chronic diseases. Remak's views, definitions and therapies are all described in his textbook, published in 1858; a French translation was presented by Horpain in 1860.

It is useful to recognize that the manner of using direct current therapeutically varied considerably among practitioners. In all cases the current was applied to the body with electrodes moistened with water; but their method of application, and how the current was delivered, often depended on individual preference. In some cases fixed (stabile) electrodes were used and the current was increased slowly to avoid unpleasant skin sensations and muscle stimulation. The current was decreased slowly to terminate the treatment. In other cases a roving (labile) electrode was used, which was passed along the skin surface. To complicate matters, a few practitioners interrupted the current, or even reversed its direction a few times during the seance. When this was done, a strong muscle twitch and unpleasant skin sensation were experienced.

Beyond the initial recognition that direct current seemed to have magical restorative powers by its ability to twitch muscles in a human cadaver, there was need to find some physiological rationale for galvanism, or voltaism as a few called it. The great physiologist DuBois-Reymond (1848) stated that a muscle twitch is obtained only at the make and break of direct current, and nothing occurred during passage of the steady current. Other physiologists carried out experiments that indicated otherwise. Earlier, Ritter (1801) had performed an interesting experiment in which direct current was passed from one hand to the other and discovered that the muscles in the hand near the negative electrode became stiffened (i.e. partially contracted), while those in the other hand near the positive electrode were very easy to move. This experiment clearly demonstrated that direct current was capable of producing a physiological response. Despite this clear demonstration, many textbooks of that era repeatedly stated that the direct or galvanic current exerted its effect by improving nutrition; but no references were provided to support this statement.

An explanation of Ritter's experiment came from Pfluger (1859) who showed that when direct current flows through a nerve,

the region under the negative electrode exhibits an increased excitability; while that near the positive electrode exhibits a decreased excitability. Thus the phenomena of catelectrotonus and anelectrotonus had been discovered and showed that galvanic current had two physiological effects. Later two interesting experiments reported by Poore (1876) in England probably did much to sustain the galvanic enthusiasm. The experiments consisted of having a subject hold his arm horizontally with a weight of 17 ounces in the palm After a measured time, the patient felt pain and could not continue; but when a constant descending current was applied, the endurance time was nearly doubled in one subject and greater than 25% more in others, despite the fact that the galvanic current was applied only about 10 minutes after the first trial.

In another series of experiments, Poore demonstrated an increase in the force of muscular contraction with a descending current. Using a squeeze dynomometer, he found that the average force for a number of squeezes was increased 25 to 50% when compared to control measurements. He even demonstrated that applying the current intermittently before selected squeezes, the force of the ensuing squeeze was increased substantially.

General Galvanism

General galvanism consisted of placing the positive electrode on the head and the negative electrode on the epigastrum or sacrum. The current flowed for 1 or 2 minutes and great emphasis was placed on the use of low current. The indications for use of this therapy were insomnia and pain. However, catelectrotonus (negative on the head) was recommended for daytime drowsiness. Other indications for central catelectrotonus were nervous derangement, relief of the wretched state of persistent drunkenness, overeating and excessive smoking. Very many treatments were required in the latter case.

La Beaume (1826) provided the following guidelines for galvanic treatment. He wrote: "The degree of Galvanic power that I dispense depends on the peculiarity of the case and the susceptibility of individuals; I have, in some instances, imparted the force of two hundred and eighty pairs of plates; in others, not more than three or four. In some cases I have continued the application for an hour and a half; and in others, not more that a few minutes. It is also of importance to minutely observe the immediate effects of Galvanism on the countenance and feelings of the patient, in order to judge if an adequate excitement be produced. I have already said, that no violent or painful sensations will be occasioned by Galvanism, if judiciously employed; when it is otherwise, the cause should be attributed to the ignorance of the operator, or to the wrong position of the conductors." In modern terms the intensity used varied between about 2 and 300 volts.

LaBeaume distinguished between the initial and subsequent effects of galvanic current. Describing the former, he wrote:

"The immediate sensations usually produced by the administration of Galvanism are, a warmth about the parts to which the conductors are applied; sometimes heat, titillation, and a gentle irritation of the skin; a feeling like that of a passing current, or an occasional dropping of water; flashes of light; a metallic taste; increased secretion of saliva in the mouth and throat; occasionally a disposition to cough; an agreeable thrill through the body; pulsations at the part; and, oftentimes, a general glow through the frame.

"The subsequent effects generally experienced after the application of Galvanism are, a glow in the body; warmth in the hands and feet, and a gentle perspiration; the abatement or removal of uneasy sensations; composure or exhilaration of the animal spirits; better appetite and improved digestion; sound and refreshing sleep; and increased discharges from the bladder and the bowels. In other cases it occasionally produced those feelings which are commonly called bilious, but which very soon subside."

The regimen prescribed by La Beaume was: "The frequency of the Galvanic application must also depend on those circumstances to which I have before alluded; a daily administration is at first necessary, till some decided effects are produced: after which, Galvanism has been exhibited three or four times a week, and then occasionally as it was found necessary. After a few applications of Galvanism, I am generally enabled to judge how long it will be necessary to continue its use."

Finally, La Beaume alerted the practicing physician to the illegitimate users of galvanism by writing:

"As I deprecate every species of quackery, and reprobate the conduct of those empirics who impose on the credulity of the public, and, by their profound ignorance of medicine and surgery, destroy the constitutions and lives of their fellow creatures; so do I condemn the practice of those charlatan-electricians, who are merely mechanical operators, and who are perfectly unacquainted with the physiology and anatomy of the human frame, the nature and treatment of disease, and the medical properties of Electricity and Galvanism, and yet proclaim them as panaceas for all diseases, and apply them at random to every case that unhappily comes within their reach."

There soon arose a modification to general galvanism that consisted of slowly moving the moist head electrode down the neck and back. One can conclude that, with this procedure, the varying electrode-subject resistance would cause the current to vary and considerable sensory stimulation would be encountered due

to cutaneous-recepter and dorsal-root stimulation.

The Electric Bath

A popular form of generalized galvanism consisted of placing a patient in a tub (5'6" long), made from insulating material, e.g. porcelain or wood) and filled with water. The patient reclined on a back rest with the head out of the water. Direct current was passed through the water via plate electrodes (12X18") at the head and foot of the bath. The electric bath first used direct current; faradic and sinusoidal alternating current were used much later. With direct current the headward electrode was positive; this polarity was found to be more relaxing than the opposite. According to Jones (1920), with tap water, warmed to body temperature, about 1/10 of the total bath current flowed through the subject. The current was monitored with a milliammeter; but the current was initially set by the therapist who placed his hand in the water to test the sensation. The final current was adjusted on the basis of the patient's response, since sensation threshold varied considerably among patients.

It is easy to imagine the wonderful tingling sensation experienced by the patient, who could easily convince himself that something good was happening. A possible benefit of the bath was deduced from an experiment conducted by Humphry Davy (1807). He found that if he immersed his fingers in a glass vessel filled with distilled water connected with the negative pole of a galvanic battery, alkali was excreted from his body and deposited in the pure water. However, if the positive pole was in contact with the water and finger, then phosphoric, sulfuric, and hydrochloric acids were deposited, and could be detected in the water.

The concept of electrolytic removal of substances by galvanic current was embraced immediately and it was believed that the electric bath would extract poisonous metallic ions and disease organisms from the body. This concept obviously attracted many and the bath became popular. Indications for its use were general debility, a variety of types of paralysis, disorders of the liver, spleen, kidneys, heart, spinal column, scrofula, dyspepsia, bronchitis, deficient nutrition and growth in infants, as well as treatment for a variety of tumors and poor eyesight.

Perhaps to improve the therapeutic efficacy, Hayes (1877) increased the bath temperature from 98 deg. F. to less than 110 deg. F. He advocated a 5-30 minute treatment. To overcome shyness, especially in ladies, he suggested covering the patient with a flannel sheet which was allowed to become wet. He reported successful use of the electrothermal bath for 15 years.

While there perhaps was a rationale for the galvanic bath, it is difficult to invoke the same rationale when the induction coil or alternating current were used with it. The effect could only be stimulation of all excitable tissues and the hazard of ventricular fibrillation is clearly apparent. Perhaps the fairest statement about the electric bath was made by Garratt (1860) who wrote, "But to deny that the electrochemical bath is devoid of all effects on the human body aside from the extraction of metals, is at best folly; yet at the same time there are the strongest reasons for doubting its utility or safety as it has been thus far tested. More than one instance has come under our own observation of the injurious consequences attending this unphilosophical use of galvanic power."

Localized Galvanism

Probably because it appeared more logical to direct the current to the ailing part, localized galvanism became more popular than generalized galvanism. One electrode was often placed over the affected organ, the other over the nerve supply to it. The brain however was a favorite target for galvanism. Electrodes were arrayed forehead-to-ecciput or mastoid, transtemporally, ear-to-ear, and apex-to-ecciput.. With a unilateral application, hemicrania (one-sided headache) was supposed to be cured. The same complaints described under general galvanism were treated with cranial electrodes. Other indications were cerebral anemia or hyperemia, hemiplegia, tic doloreux and many diseases of the eye and ear.

With localized galvanism, the current was derived from a battery of 5-25 cells and flowed for 1-10 minutes. With low current applied to the head, the patient would feel warm and somnolent. With higher current, dizziness and unpleasant sensations, including the perception of flashes of light, were produced. Sometimes vomiting, blindness and even convulsions occurred.

Virtually all of the cranial nerves received galvanic treatment. For a diminished sense of smell, the ofactory nerve was stimulated with a nasal electrode. For poor vision, the optic nerve was treated with an electrode near the weak eye. Impaired audition was treated by applying a galvanic current to an electrode in the water-filled ear canal. A stimulating electrode was placed below the tongue to treat impaired taste. The spinal cord was also treated with galvanism. The anode was placed over the suspected vertebra and the current returned via an indifferent electrode. Typically 15-60 cells were used to deliver current for about five minutes, during which a prickling sensation was experienced. The indications for spinal treatment were ataxia and amenorrhea. An electrode was placed in the rectum to treat "intestinal atony" (constipation) and excellent results were claimed for prostatic infection using an urethral electrode. Pneumogastric (vagus) and cervical sympathetic nerves were treated with galvanism, as were peripheral

nerves and muscles. The vagus nerve was treated for two minutes with the cathode at the angle of the jaw and the anode on the manubrium. The indications for treatment were asthma, spasmodic diabetes and "certain afflictions of the heart" (Althaus 1873). The cervical sympathetic nerve was treated with one electrode on the auriculo-maxillary fossa, and the other electrode on the sixth or seventh vertebra on the opposite side. Considerable dispute was associated with this electrode placement, since other nerves intercepted the current path. Nonetheless it was believed that the circulation to the eye, ear, face and part of the brain was improved.

Galvanism of the peripheral motor nerves employed two techniques; with one the spinal cord was included and with the other it was excluded. When excluded, the cathode was placed over the nerve nearest to the spinal cord and the anode was over the nerve or muscle. When the spinal cord was included, the anode was placed over the spinal column at the appropriate level and the cathode was over the nerve or muscle. The indication for this therapy was paralysis.

Cardiorespiratory Resuscitation

Galvanotherapy was recommended for emergency resuscitation. A frequent occurrence was asphyxiation from coal-gas fumes - prevalent because of the industrial revolution. The resuscitative procedure of that day is well described in Good's (1836) textbook of medicine. He wrote:

"If insensible, cold water should be dashed on his face; strong vinegar, and especially aromatic vinegar, be rubbed about his nostrils, and held under them, and stimulating clysters (enemas) be injected, as recommended under the first variety. The lungs should be inflated with the warm breath of a healthy man, or which is better, with oxygen gas."

It is quite clear that what we now call mouth-to-mouth respiration was used at that time, as was oxygen therapy.

Good advocated use of the voltaic battery, which delivered electric fluid (current), as a resuscitative adjunct. He wrote: "A proper use of voltaic electricity is also in many instances found highly serviceable. No advantage, however, is likely to accrue from passing the electric aura across the chest, directly through the heart and lungs, which is a common practice. The fluid should be transmitted along the channel of the nerve, from the seat of the diaphragm, or that of the par vagum immediately under the sterno-mastoid muscles, and that of the great sympathetic nerve, which sends forth branches to the heart."

He went on to cite case reports of successful respiratory resuscitation with the voltaic battery. The procedure was similar to that to be described for respiratory and cardiac arrest sometimes encountered during surgical anesthesia.

In the latter part of the nineteenth century, the favorite anesthetic was chloroform, probably because it provided a smooth induction. However, in common with all anesthetics, it depresses respiration; but it has another nasty side effect, namely it is vagotonic. Therefore respiratory depression and often arrest, as well as cardiac arrest, were not uncommon in surgical procedures and the anesthetist had to be vigilant. To make matters worse, resuscitation procedures were at best limited. Thus, it was not unnatural that the reanimative powers of galvanism were considered and it was applied with remarkable results. Perhaps the best account of galvanic cardiorespiratory resuscitation was presented by Green (1872), a surgeon who routinely used chloroform. He kept a galvanic battery "at the ready" in the operating room (theatre) and in the postscript to his paper in the British Medical Journal, he stated that "One pole should be applied to the neck and the other to the lower rib on the left side." The following excerpts from Green's paper will indicate the responses obtained in seven cases.

The first case was an elderly woman in whom the pulse and breathing suddenly ceased as the chloroform was being administered. "Galvanism was then tried; it produced some convulsive efforts of the respiratory muscles, but animation was not restored."

The second case was an elderly woman. "After a short inhalation of the first drachm, a few convulsive respirations were followed by the sudden stoppage of the heart's action and of breathing...Galvanism, artificial respiration, etc., were at once tried; the first caused strong contractions of the face and trunk, but had not the slightest effect on the heart; the latter was kept up for nearly half an hour, through an opening of the trachea, but without any effect on the heart."

The third case was a boy who had been operated on successfully and the surgeon was about to leave the operating room. "On turning around, I found the boy deadly pale and pulseless and his breathing stopped. The galvanic battery was in the theatre ready for use, and it was instantly applied. After a few seconds both pulse and breathing returned."

The fourth case was an elderly man. "A small quantity of chloroform had been given when the pulse suddenly stopped and the man appeared dead. The galvanic apparatus was near and was instantly used. A deep and rapid inspiration, succeeded by a strong noisy expiration like a loud groan, was the immediate result, and at the same time he started up into the sitting position. The circulation was at once restored and he entirely recovered."

The fifth case was an elderly woman. About one half hour into the operation "the pulse suddenly stopped, and to all around she appeared dead. Galvanism was instantly applied, with the same result as in the last case. Circulation and respiration were instantly restored."

The sixth case was a boy. "A small quantity of chloroform was given, when suddenly the pulse became hardly perceptible, but did not stop entirely. Galvanism was at once used by Mr. Crisp of Swallowfield, then house-surgeon, and an instant recovery was the result."

The seventh case was a girl. "Chloroform was being given, when suddenly the pulse stopped. Galvanism was at once used and instant restoration was the result."

It is quite clear that the intermittent application of galvanic current twitched the respiratory muscles, stimulated cutaneous receptors and may have stimulated the ventricles each time it was applied. It was not uncommon to use a battery of over two hundred cells (pairs) which represents a stimulus of over 300 volts. Although the mechanism underlying these resuscitations will never be known, the events attracted considerable attention and demonstrated that electric current could be used for resuscitation. When faradic current became popular, it was also used with similar results, but with a new hazard, which will be discussed later.

Direct-Heart Cardiac Pacing

Steiner (1871) also pointed out that cardiac arrest was a frequent complication of chloroform anesthesia. He stated that the heart could be made to beat by galvanopuncture. To demonstrate this fact, he overanesthetized horses, dogs, cats and rabbits to produce cardiac arrest. Heart action was witnessed by thrusting a needle through the left thorax into the ventricles. Each time a heart beat occurred, the needle moved visibly. When cardiac arrest occurred, he applied intermittent galvanic current to the needle to evoke a contraction; Figure 3-5 illustrates the author's concept of the technique. Steiner recommended applying "the positive pole to the needle in the heart, the negative pole in the pit of the stomach or on the left side of the breast in the 7th intercostal space." It is quite clear that Steiner had intentionally paced the chloroform-arrested heart.

Closed-Chest Cardiac Pacing

The cardiac analog to Alexis St. Martin and Beaumont is Catherina Serafin and von Ziemssen. Catherina was a 42 year old woman who had a very large defect on the anterior left chest wall due to resection of a cartilagenous tumor. The heart was covered only by skin and was both visible and palpable. Seizing the opportunity, Ziemssen (1882) made smoked-drum kymographic records of the movements of the aorta, pulmonary artery, atria and ventricles using the Marey receiving and writing tambours, which were described much later (1885). After recording normal movements of these structures, Ziemssen placed stimulating electrodes at various sites on the skin above the heart and, occasionally over the left scapula. He used interrupted galvanic current to perform what now would be called closed-chest cardiac pacing.

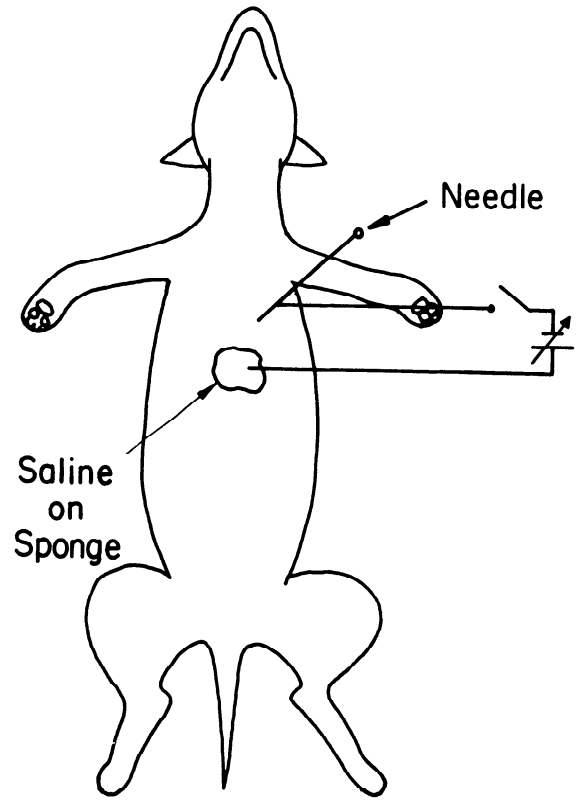


Figure 3-5. Steiner's method of pacing the chloroform-arrested heart by galvanopuncture.

Ziemssen used a 10-element (cell) battery (about 15-20 volts) and a rheostat to control the current intensity. He also used a metronome to inscribe time marks on the smoked-drum record, as well as to time the intermittent application of galvanic current. In most of his experiments he used 120 stimuli per minute; but occasionally used 140 and 180. Figure 3-6 (his figures 22, 23 and 24) illustrate cardiograms of the heart beating normally (to the left of the downward arrow) and during rhythmic galvanic stimulation (between the arrows). Figure 3-6A represents stimulation at 120/minute and Figures 3-6B, C represent stimulation at 140 and 180/minute respectively. In the latter case, Ziemssen remarked on the pulsus alternans provided by the rhythmic stimulation.

It is obvious that Ziemssen achieved closed-chest cardiac pacemaking in a human subject. It is unfortunate that he did not pursue this therapy for pacing the many hearts arrested by chloroform anesthesia.

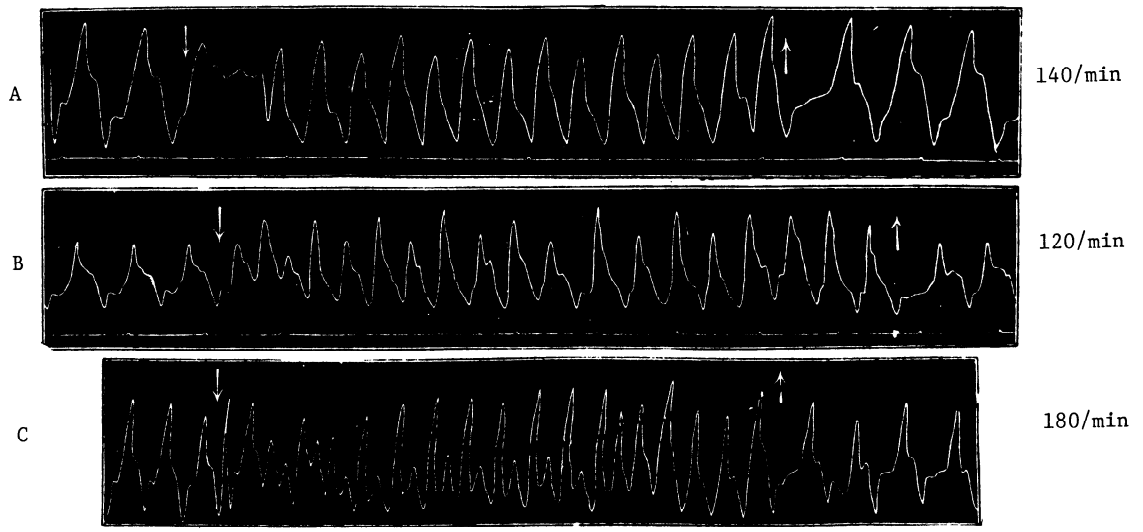


Figure 3-6. The first examples of closed-chest cardiac pacing showing kymograph records of the heart movements in Catherina Serafin. A illustrates pacing at 120/min, B at 140 and C at 180. Timing of delivery of the intermittent galvanic stimuli was accomplished with a metronome. Pacing was started at the downward arrows and terminated at the upward arrows. The time marks are 1 sec. apart. (From Ziemssen 1882).

Galvanic Cautery

The term "Galvanic Cautery" was used by practitioners rather indiscriminately. Some meant the application of direct current to heat a thin platinum wire using the battery in the galvanic apparatus; others meant the application of direct current to an accupuncture needle. In the latter case, both electrolysis and a thermal lesion were produced. Galvanopuncture was the name given to this technique.

The electrically heated thin platinum-wire cautery appeared in the mid 1800's and took many forms. The galvanic battery was used to provide the heating current. Circular and elliptical loops were standard, as was a v-shaped wire thermode. The thermal cautery was used for coagulation and cutting in the manner performed with the modern radiofrequency electrosurgical unit.

An interesting technique was used for removal of a tumor or polyp. Short lengths of thin platinum wire were passed through the growth with the two ends protruding. The battery was connected to the ends and the wire was heated to destroy the tissue. Sometimes, several wires were used and they were left in situ until suppuration occurred, at which time they were easily removed. Later the tumor fell off, being devoid of a blood supply.

Galvanopuncture

The fascinating and extensive history of electropuncture (galvanopuncture), the method of applying direct current to produce a thermal lesion or electrolytic lesion, was reviewed by Beard and Rockwell (1891). Essentially, the goal was to achieve electrolysis by passing direct current through a needle electrode in the affected tissue. Sometimes the monopolar technique was used in which one or more needles (connected in parallel) were in the tissue. The return path for the current was via a moist sponge electrode on the skin at a convenient site. At other times a bipolar technique was used in which two needle electrodes constituted the anode and cathode in the tissue to be treated. When the monopolar technique was used, the needle was usually made positive. The needles were of bare gilded steel, contacting the tissue throughout the immersed length. Typically, a battery of 10-15 cells was used. The effect of polarity was described in terms of acidic and alkaline, the former occurring at the cathode and the latter at the anode. Although tissue destruction appeared to be most noticeable at the negative pole, the response at the anode was substantial. Chemical destruction of the tissue occurred and the degree was controlled by selection of the current intensity and duration of flow.

Perhaps the best illustration of the nature of electropuncture comes from Althaus (1875) who described his observations while removing a nevus using two needles in the tissue to be treated. "As soon as the connection is made, a destruction of the texture of the nevus is seen to commence, the blood vessels and the skin withering away rapidly under the eyes of the operator. The destruction is more thorough at the positive than at the negative pole, and the worst parts of the nevus should therefore always undergo the influence of the former. As a rule, not a drop of blood is lost during the operation; but if, by sudden movement of the child one of the needles should come out prematurely and a drop of blood could appear, this can be immediately coagulated and any hemorrhage checked, by applying the positive pole to the puncture."..."When everything morbid appears to have been electrolyzed, the action is discontinued and the surface

covered with a piece of gold-beater's skin. There is no pain or discomfort after the operation; no dressing is required, for there is no discharge; the scab remains dry and falls off in ten or fourteen days, leaving the healthy surface which gradually assumes the appearance of the surrounding skin."

Galvanopuncture, or electrolysis as it became designated, was used for the removal of skin blemishes such as warts, moles, and nevi. The only other available treatments employed caustic solutions or surgery. In the former case there was the risk of poisoning and in the latter, blood loss was common. Thus galvanopuncture could compete well with both therapies. According to Beard and Rockwell (1891), galvanopuncture was used effectively to remove malignant tumors of the breast and palliatively to treat inoperable tumors. Hard tumors were the most difficult to treat, cystic tumors the easiest.

A considerable activity was devoted to treating aneurisms with multiple needles. For this technique the goal was to induce a blood clot which would in turn result in a deposit of fibrous tissue. The use of galvanopuncture to treat aneurisms appears to have originated in the late 1840's. According to Courtot's medical thesis (1847) it was well known that when galvanic current was passed through electrodes in the white of an egg, coagulation occurred at the anode and a transparent gel was produced at the cathode. Moreover Courtot stated that Clavel had reported in his medical thesis of 1847 that a flow of galvanic current delivered via a needle electrode for one minute would completely close the femoral artery of a dog. Thus the clot-inducing properties of galvanic current had been well established. From this time a considerable interest was directed toward the use of galvanopuncture to induce clot formation. Courtot stated that an Italian commission had been organized to study the subject and reported that the negative pole introduced into an artery had no coagulating property, but the positive pole induced clot formation.

It is not difficult to understand development of the logic of applying galvanopuncture to the treatment of aneurisms, for which the only medical therapy was prolonged bed rest and hope, with perhaps a little prayer. Although the ligature could be used with some superficial aneurisms, surgeons had limited success with this mode of therapy. Intra-abdominal and thoracic aneurisms were untreatable. At that time it began to be recognized that the induction of an electrolytic lesion in the inner wall of the aneurism would result in a clot. Some believed that it was inflammation produced by the chemical lesion that produced the clot; others believed that it was the positive electrode that induced the clot formation at the electrode site. Nonetheless it was known that the clot resulted in an ultimate fibrous tissue deposit which could strengthen the wall of the aneurism.

There is such a wealth of literature on galvanotherapy for treating aneurisms that space permits inclusion of only a few accounts of the therapy. An excellent editorial on the merits of galvanopuncture appeared in the British Medical Journal (1873).

One of the earliest reports describing galvanopuncture for human aneurisms is due to Petrequin (1849) a surgeon in Lyon, who reported the successful treatment of a fist-sized aneurism in the popliteal region of a 65-year old man. The pulsations could be easily palpated and the aneurism exhibited a bruit on auscultation. The tumor prevented the knee from bending.

Petrequin inserted 4 needles into the aneurism so that they crossed within it. Using a voltaic battery, the current was passed through the needles in succession. After 16 minutes of current flow, and in the presence of 6 physicians and surgeons, the tumor was found to be hardened. The needles were removed and the patient returned to bed. The tumor was examined daily and by the third day it had decreased in size. By the thirteenth day the tumor was further decreased in diameter and circumference and the patient regained relatively normal leg motion. Petrequin (1850) went on to apply the technique to other patients and recommended the optimal placement of electrodes, namely at the corners of a rectangle circumscribing the aneurism; two electrodes were placed parallel to the aneurism and two were placed diagonally.

Another interesting method of applying galvanopuncture to treat an aortic aneurism was described by Lusk (1912) of New York. He wrote, "The patient had been struck on the right hip by the mud guard of a rapidly moving taxi." The surgeon found "a pulsatile expansile tumor protruding a little above the surrounding skin level at the right edge of the sternum, having eroded through the right second costal cartilage and adjoining portion of the sternum. Crepitus felt with expansile pulsation over middle sternum. Bruit. A little thrill on exertion."

The treatment consisted of forming a length of thin gold-platinum wire (28 gage) into a coil, the diameter of which was equal to that of the aneurism. The wire was threaded through a needle (passed through the skin into the aneurism) so that it formed a coil within the aneurism and contacting its walls. Direct current was passed through the wire electrode which was positive with respect to a sponge electrode on the neck. The current program started with 100 mA for 15 minutes and then reduced to 50, 40 and 30 mA each for 15 minutes. At the end of the treatment period, the needle was withdrawn and as much of the wire as would come was withdrawn and cut off.

By the tenth day, the pulsation was

markedly reduced. By the twenty-fifth day, the tumor was "little expansile". Three months later the patient could walk upstairs "with perfect comfort and he feels perfectly well, no pain. The superficial tumor is practically obliterated, evidencing shrinkage of the sack. Pulsation can still be felt, though, but very little expansile, and a bruit is still heard, showing that the sack is not obliterated. The aneurism reached its present state of quiesence about eight weeks after the operation period."

Galvanopuncture therapy for aneurisms probably would have continued had surgery not made the great advances it did. However the apparently bloodless technique of using direct current to induce a clot should not be cast aside too readily, for there are many instances when clot induction may be highly desirable.

Bone-Fracture Union

Although galvanopuncture was used to destroy tissue and promote clot formation, it was also used to promote the union of bone fractures that failed to close, despite all immobilization and splinting efforts. Galvanotherapy, which is still used today for fracture union, dates from Boyer's (1816) text on surgical diseases. A translation by Stevens contains descriptions of several cases in which the galvanic current was passed transverse to and along the fracture line. In one noteworthy case of a fracture that failed to unite after thirteen months, the galvanic current was applied daily. "At the expiration of two weeks the limb had become evidently less flexible in the situation of the fracture and after a continuance of the same treatment for six weeks, the man was able to walk and leave the hospital cured." Unfortunately, no description was given of the electrodes, the number of cells and the duration of each treatment.

The technique of galvanopuncture was used with considerable success by Lente (1850) in three cases of non-union. He used Pikes galvanic apparatus connected to accupuncture needles, "the needle being passed in the periosteum on either side of the fracture." The first case was a fracture at the middle of the left femur of an adult girl. From August 9, 1849 to January 25, 1850, the fracture did not unite, despite immobilization and splinting. Galvanopuncture was then applied thrice weekly. By March 10th 1850, consolidation was occurring and by April 1st 1850 the union was firm. Despite uncooperativeness, by May 21, 1850, the patient was able "to hobble about the house" and was discharged.

Lente's second case was a simple fracture of both bones in the left leg of a nursing mother, the accident having occurred on May 11, 1850. Splinting was applied; but no union had occurred by July 20, 1850. On that day galvanopuncture was started and applied every other day for ten minutes. On August 19th 1850, Lente wrote, "The union of the fracture is quite firm and as the patient desires to go home, she is today discharged."

The third case was a simple fracture of both bones in the right leg of an adult male, the accident having occurred on May 2, 1850; union had not occurred. Galvanopuncture was then applied daily. By July 15, 1850, he wrote, "union of fracture becoming more firm. Ordered to apply electrically on alternate days, July 15, union now firmly consolidated. Discontinue application. Patient allowed crutches with the limb protected by the starch splint. September 1st. Discharged, cured."

Lente's results were not embraced by physicians who adopted harsher methods for treating non-union. Lente cited the methods as "rubbing the ends of the bones together, the introduction of the seton between the fracture ends, etc." (A seton is a tape or thread drawn through the skin designed to maintain an opening for drainage). As an alternate to these procedures, Lente recommended "Electricity, by the ordinary galvanic apparatus, is easy of application, not very painful, and in no way dangerous; it is therefore one which, I think, should always precede the other means. But to be at all effective, it must be applied in connection with accupuncturation. It appears to have little or no effect when the poles of the battery are applied merely to the soft parts on either side of the fracture, as the current does not appear to reach the bone at all".

Perspective

Beyond its ability to produce a muscle twitch, there is no doubt that many interesting uses were found for the application of galvanic or direct current. It is doubtful whether generalized or localized galvanotherapy, applied with body-surface electrodes, produced beneficial effects beyond making some patients feel exhilarated - although hysterically depressed function was restored frequently. Such "cures" provided benefit to patients and impressed physicians who perhaps were not fully aware of this condition. Surprisingly, the electrotonic effect of direct current to "refresh" muscles and to increase endurance was not exploited. However, galvanopuncture produced impressive results. It was the only treatment for aneurisms for a while. Its ability to promote bone-fracture union is still in use today.

The use of intermittent galvanic current applied to a chest and neck electrode to twitch the respiratory muscles and likely evoke ventricular contraction was life-saving in cases of respiratory and cardiac arrest due to chloroform anesthesial. The technique was also safe and probably abandoned when this anesthetic was replaced by others.

Chapter 4. The Inductorium Stimulator and Faradic Therapy.

The Inductorium

It is generally accepted that Du Bois-Reymond introduced the induction-coil (inductorium) stimulator to physiology in 1848. Figure 4-1 illustrates one of his instruments which was duplicated and improved many times during the latter part of the nineteenth century. The inductorium became the essential tool for stimulating excitable tissue. Although these facts are well known, DuBois Reymond was not the first to use the Inductorium to stimulate animals and man. In fact, development of the induction coil (and transformer) as physical devices was aided by noting the muscular response when using it as a stimulator, there being no instrument to measure the output of such devices.

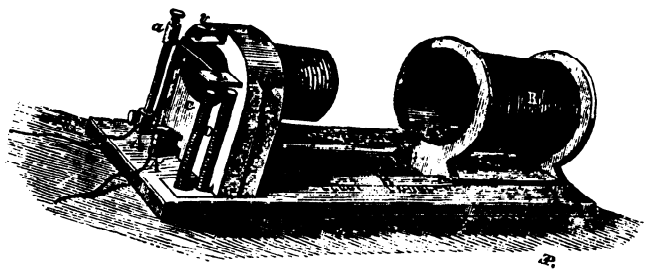


Figure 4-1. The DuBois-Reymond inductorium with separate current interrupter (D). (From Fleming. The Alternate Current Transformer 1900).

A few comments are in order regarding the two types of stimuli produced by the inductorium and the terms used to describe them. The two types of stimuli result from the manner in which the inductorium is used, namely without or with an automatic current interrupter in the primary circuit.

The essential components of the inductorium stimulator are shown in Figure 4-2. The device consists of two coils, a primary coil of a few tens of turns and a secondary coil of many more. The primary coil was wound on a bundle of insulated iron wires, thereby concentrating the magnetic field due to the primary current. The magnetic coupling, and the output available from the secondary, were controlled by adjustment of the distance between the two coils. When a battery (E), i.e. direct current, is applied to the primary, a magnetic field of increasing intensity is produced immediately. Figure 4-2 illustrates the current (I) in the primary coil when the voltage is applied (M). This changing field, due to the rise in current, induces a voltage (e_o) in the secondary. When the primary current reaches its steady value, the magnetic field is no longer changing and no voltage is induced in the secondary. When the primary current is interrupted (B), the magnetic field diminishes instantly and a very high voltage of the opposite polarity is induced in the secondary. Thus a small voltage pulse appears when the current is made to flow in the primary; a much larger voltage pulse is delivered when the primary circuit is broken, as shown by e_o in Figure 4-2. The time (C) between the make (M) and break (B) shocks is determined by the time of initiating and breaking current flow in the primary coil.

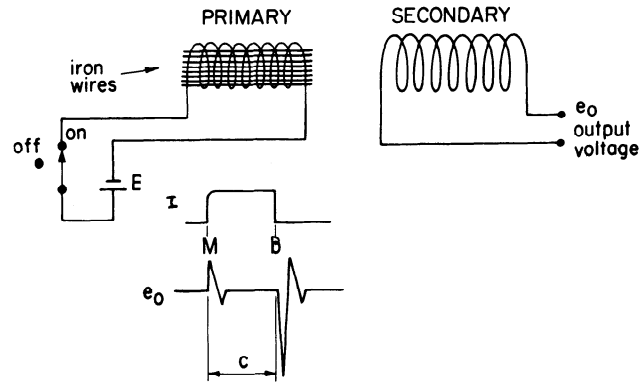


Figure 4-2. The make (M) and break (B) shocks provided by the inductorium.

Often it was desirable to deliver only the strong break shock. This was accomplished by first placing a short circuit across the secondary coil and then applying a current to the primary coil. The short circuit was then removed from the secondary and the break shock was delivered when current flow in the primary circuit was interrupted.

The second method of using the inductorium consisted of placing an automatic current interrupter in series with the primary coil. Figure 4-3 illustrates this arrangement with the current interrupter contact (I) on the armature (Ai) opposite the iron-wire core of the inductorium. When a battery E, (direct current) is applied to the primary coil, current flows through the contact on the armature and establishes a magnetic field in the core. This also produces the make shock across the secondary terminals. However, the magnetic field attracts the armature (Ai) and the primary current is interrupted. In this way the break shock appears across the terminals of the secondary coil. When the induction coil is operated in this way, the vibrating armature current interrupter causes a train of small make and larger break shocks (e_o) to appear across the terminals of the secondary coil. The frequency of the train of pulses depends inversely on the mass of the armature (Ai) and directly on the stiffness of the leaf spring (L) that restores its position when current flow ceases. Stimuli with a frequency of perhaps 20 to 200 per second were attainable. The duration of the make and break shocks were in the range of a fraction of a msec to a msec, depending on the design of the inductorium. When these stimuli were applied to skeletal muscle or a motor nerve, a tetanic contraction resulted. The term faradic stimulation

was often used to denote that a train of pulses was used as the stimulus.

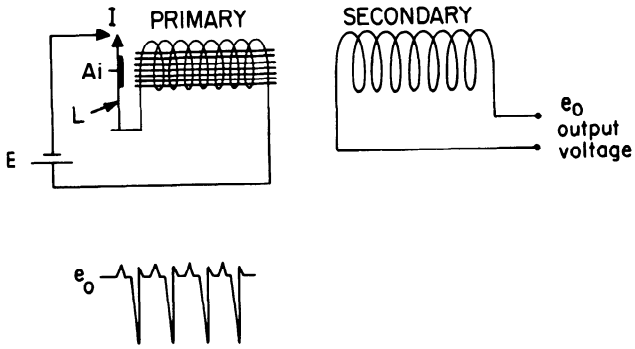


Figure 4-3. The inductorium with a magnetically-driven current interrupter in series with the primary coil. This arrangement provided delivery of a train of make-break stimuli, e_o. Such a train was called a faradic stimulus.

History of the Inductorium

Faraday in the U.K. and Henry in the U.S.A. described magnetic induction independently and almost simultaneously around 1831. Following discovery that a change in magnetic field could induce a voltage in a wire or coil, there occurred an intense interest in creating the most efficient induction coil, efficiency being defined as production of the strongest shock. Parenthetically, in 1819, Oersted had discovered that a current-carrying wire produced a magnetic field which could interact with the magnetic field of a permanent magnet, causing it to be displaced if suitably suspended. Thus the basic ingredients for the creation of the induction coil were at hand. Leading the efforts to create the most efficient induction coil was the Reverend J. Callan, Professor of Natural Philosophy at the R.C. College, Maynooth, England. Addressing himself to this task in 1837, he identified the key factors that influenced production of the strongest shock; they were: length and diameter of the wires used for the primary and secondary coils, the voltage (number of cells) applied to the primary, the distance of the coils from the iron core, the orientation of the coils with respect to the axis of the iron core, the importance of insulation on the wire that constituted the coils, and the thickness of the iron core. Having found the optimum among these factors, he fabricated a horse-shoe shaped magnet. The strength of the magnetic field therein was measured by the force necessary to remove a bar (keeper) placed across the ends of the horse-shoe shaped electromagnet as shown in Figure 4-4A. The magnetic circuit was made from a bar of iron, 1 1/4 inch thick and 2 feet long. The primary coil was wound with copper wire 1/12 inch in diameter and 50 feet in length. The secondary was wound with iron wire 1/40th of an inch in diameter and 1300 feet in length.

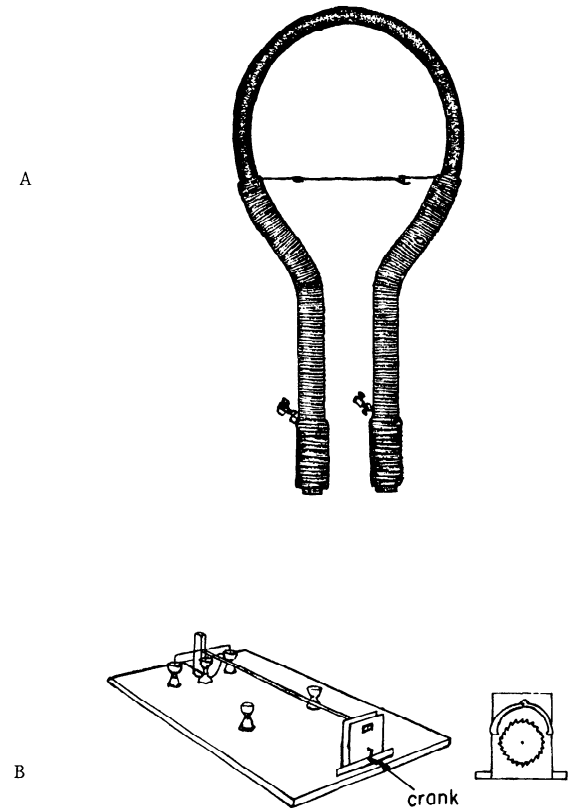


Figure 4-4. The induction coil (A) developed by Callan (1837). From Fleming. 1900 Vol. 2. B is Callan's hand-cranked current interrupter.

Callan connected hand-held electrodes to the secondary (iron-wire) coil and connected a (voltaic) cell of 7- inch plates to the primary (copper-wire) coil by an ingenious mechanical current interrupter (Figure 4-4B) which employed mercury-filled cups. He stated, "The shock was intolerable." Not content with an intolerable shock, Callan built a stronger induction coil which he made using an iron bar 2 1/2 inches in diameter which weighed 15 stone (210 pounds). With the primary of this coil connected to a battery of 20 voltaic cells via his hand-cranked current interrupter, he wrote, "For when it (the output) was passed through the body of a large fowl instant death was produced." Pressing on, he stated "From the helix of the large electromagnet which I am now making I expect to obtain an electric current equal in point of intensity (voltage) to that of a battery containing several hundred thousand voltaic cells."

Iron-Wire Core

The first induction coils consisted of wire wound on an iron bar, usually having the shape of a "u". The efficiency (output) was judged by the strength of the electric shock or the tiny sparks produced when the two secondary wires were arranged to form a spark gap. Often the gap consisted of a slender carbon rod placed above a pool of mercury. It was found that as the rate of current interruption

in the primary was increased, the output voltage decreased. Sturgeon (1837) evaluated the effectiveness of different cores ranging from an iron bar, gun barrel, bundle of iron tubes, rolled iron foil, and finally a bundle of iron wires. The latter was found to be extremely effective and the spark did not diminish beyond 60 current interruptions per second. Apparently Bachhoffner (1837, 38) was carrying out contemporary experiments in which he found that the efficiency of the coil was increased when each iron wire in the bundle was insulated.

We now know the reason for the superiority of the bundle of insulated iron wires. Just as a voltage is induced in the secondary coil, it is also induced in the core and causes large short-circuit (eddy) currents to flow therein. By using insulated iron wires, the eddy currents are dramatically reduced while the magnetic properties of the core are retained. Thus, use of a bundle of insulated iron wires as the core was equivalent to removing short circuited turns.

Current Interrupter

A wide variety of devices was used to make and break the direct current applied to the primary coil. Rich as the variety was, all devices used mercury cups into which a wire dipped to make and break the primary current. The first mechanical breaker was due to Callan (1837) who coupled a rod to an escapement which engaged a toothed wheel that was turned by hand. When activated, the rod oscillated as the crank was turned. Two contracts on a crossarm mounted on the rod alternately dipped into and out of mercury cups, thereby making and breaking the primary current. Figure 4-4B is a reproduction of Callan's "repeater" which was easily capable of 60 current interruptions per second.

Hand cranking the current interrupter soon became inconvenient and various automatic electromagnetic interrupters were devised. In 1839 Page, American physician and father of the commutator, developed the first magnetically driven current breaker for the induction coil; Figure 4-5 illustrates his instrument. The core of the induction coil consisted of a bundle of soft iron wires, over which the primary coil, consisting of thick copper wire, was wound. The secondary, wound over the primary, had many turns of fine copper wire. The current breaker was a cantilever, at one end of which was a soft iron ball (called the hammer head) in front of the core. The other arm of the cantilever carried two contacts dipping into cups of mercury. The current from one terminal of the battery was led to the first cup, traveled along the cantilever to the second cup, which was connected to one end of the primary coil. The other terminal of the primary coil was connected to the other terminal of the battery. When current flowed in the primary coil, the iron ball was attracted to the iron-wire core and lifted the contacts out of the mercury cups, (m,n), thereby breaking the primary current. A counterweight (f) on the cantilever caused it to move back so that the contacts entered the mercury cups and reestablished current flow in the primary coil. The frequency of the make/break sequence was controlled by adjustment of the position of the cantilever weight f. Ingeniously, Page prevented the iron ball from sticking to the iron-wire core by interposing a thin shim of brass. The output available from the coil was capable of striking a spark 1/2 inch in length.

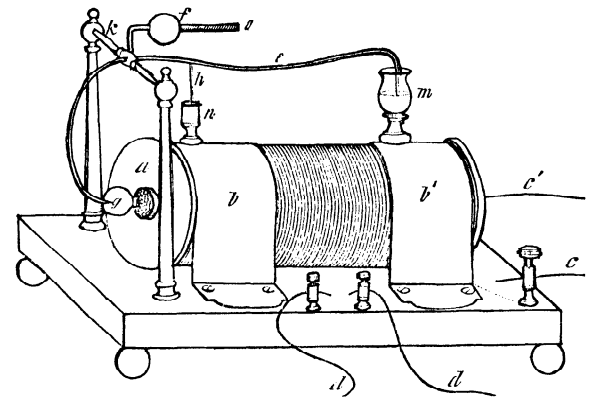


Figure 4-5. Page's induction coil (From Page, C. G. Amer. Journ. Science 1839, 35 p. 258).

Page was by no means the only scientist to develop a magnetically driven current interrupter. However, such devices were separate and all used the mercury contact arrangement to make and break the current. However, Page appears to be the first to have used the magnetic field of the induction coil to actuate the current breaker. This feature was adopted in all of the later inductorium stimulators.

The mercury-cup switch was not without practical difficulties. Due to the arc, the mercury became oxidized and some was vaporized and condensed on nearby objects. To minimize this inconvenience, Page covered the mercury with a film of oil or alcohol. This medium also served to quench the arc during the break and therefore increased the rate of decrease of current flow, thereby providing a stronger break shock.

Although the use of alcohol or oil offered a partial solution to the mercury problem, the inconvenience of mercury led investigators to develop mercuryless contact breakers which were magnetically actuated. Apparently the first to develop such a current breaker were Neef (1839) and Wagner (see Althaus 1873) who created the vibrating armature which carried platinum contacts. Figure 4-6 illustrates these devices. The moving armature of such magnetically driven devices (or electrotomes as they were called), soon carried a rod and clapper and became the trembling-armature doorbell. According to Fleming (1900) "It will be seen that by the year 1840 the induction coil had been practically completed in all essential parts, with the exception of the con-

denser. The primary and secondary circuits of thick and thin wire, the divided iron wire core, the vibrating contact breaker have been arrived at and perfected chiefly by the investigations of Callan, C.G. Page, Sturgeon, Bachhoffner, Wagner and Neef." (The capacitor referred to by Fleming was added by Fizeau (1853), to resonate the secondary coil and obtain a much higher secondary voltage. However, Ruhmkorff's name is usually associated with this configuration. It is noteworthy that although Page (1839) had demonstrated that the magnetic field of the core of the induction coil could operate the current interrupter, the induction coil developed by DuBois-Reymond (Figure 4-1) used a separate interrupter.

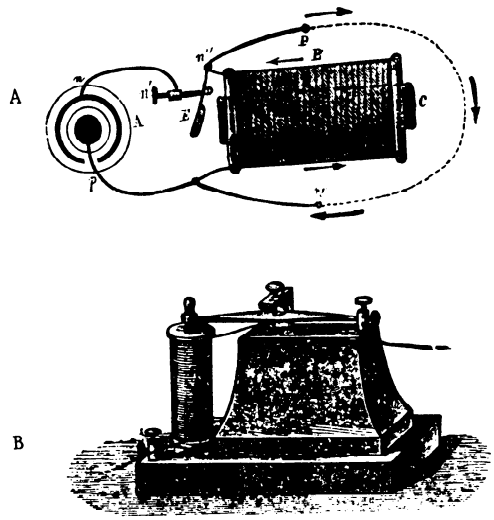


Figure 4-6. Magnetically-driven metallic contact current interrupters. A illustrates Neef's interrupter (1839) and B illustrates Wagner's. (A from Althaus 1873 and B from Fleming 1900).

In modern terminology, the induction coil delivers a train of heavily damped sine waves of opposite polarity and unequal amplitude. The inductorium resembles a constant-current stimulator with an output that, although controllable, was largely unknown in terms of current and pulse duration, which we now know to be in the msec to fraction of a msec duration range. Nonetheless the inductorium was an ideal stimulator for producing a tetanic contraction in skeletal muscle and for stimulating nerves in the central, peripheral and autonomic nervous system.

Not only was the inductorium widely used in physiological laboratories, it saw considerable service in electrodiagnosis and electrotherapy. Some of these applications were associated with medical quackery. However one interesting observation is noteworthy at this point. Duchenne (1872) noted that different induction coils gave different responses. He stated that long coils (those with many turns) produced strong sensory and motor responses when used with skin-surface electrodes. However when a short coil was used there were strong motor, but less sensory responses. The explanation is now quite clear, namely the pulse duration is long with a secondary coil of many turns, due to its higher inductance. Since, with decreasing duration of stimulus, the strength-duration curve rises more sharply for sensory receptors than for motor nerves, it is clear that the long-duration pulses (obtained with the long coil) would produce strong sensory and motor responses while the short secondary coil, with its short-duration pulses, would stimulate motor nerves and would be less capable of stimulating sensory receptors. One can only admire the careful observation made by Duchenne.

Faradic Electrotherapy

Introduction

Faradism was the name used by Duchenne (1872) to describe use of the train of short-duration current pulses from the faradic (induction) coil. In fact, Duchenne in Paris was the champion of this technique which gained popularity shortly after introduction of inductorium to physiology by DuBois-Reymond in 1848. As with the previously used forms of electric current, faradic current was applied to the whole body (general faradization) and to specific regions (local faradization) to treat a wide variety of ailments.

Before describing the various therapeutic applications of faradic current, it is useful to recognize that the physiological response is much different than that of franklinic (static) or galvanic (direct current) electricity. Because faradic current consists of a train of short-duration pulses (see Figure 4-3) it can produce a tetanic contraction in skeletal muscle; whereas static discharges from the Leyden jar and direct current produce only a twitch. Moreover a faradic pulse train can stimulate sensory receptors (and their nerves), as well as autonomic nerves. In particular, using a distorted train of sine waves, from an induction-coil stimulator, Weber (1845, 59) showed that stimulation of the vagus nerve slowed and arrested the heart rate. It came as a considerable surprise to physiologists to learn that active stimulation by faradic or sinusoidal current could inhibit an ongoing physiological event. Therefore, it was recognized that faradic current could exert a dual effect, a situation that made it very attractive for electrotherapy. Thus the inductorium made it possible to stimulate a wide variety of excitable tissues, including the central nervous system. Unfortunately, not all who used faradic current were aware of its effect on the heart, which if intense enough, is fibrillation. Nonetheless this event was apparently an infrequent occurrence in clinical practice.

General Faradization

Application of faradic current to the body in the head-foot axis was designated general faradization. Duchenne (1872)

stated, "The influence of this excitation can activate secretions and transport; for example it can be felt in such and such an organ, according to individual disposition." Thus he believed that a sensory response constituted part of the therapy in addition to the secretory action and obvious motor response in skeletal muscle.

The various textbooks on electrotherapy of the late nineteenth century are in fairly good agreement on the treatment procedure which consisted of having the patient sit on a stool without a back or armrest. The bare feet were placed on a copper electrode connected to one terminal of the induction coil. The soles of the feet were preferred for current application because of the reduced sensitivity due to the thick skin. A bowl of water containing the foot electrode was to be avoided because it may be kicked over due to the muscular contraction. The other terminal of the induction coil was connected to a copper-ball electrode, one inch in diameter, covered with a moist sponge. The therapist grasped this electrode with one hand and applied the other hand to the moistened hair on the patient's head. Thus the therapist was in series with the patient and induction coil and therefore could judge the appropriateness of the strength of the current. Figure 4-7 illustrates the technique. Sometimes the patient was contacted by a moist sponge, which the therapist held. When the therapist's hand was used as the electrode, the term "electric hand" was used to designate the procedure. Commenting on these techniques, Beard and Rockwell (1891) stated, "As the current passes through his own person the operator can judge by his own sensations whether it is too strong or too weak, and by increasing or diminishing the grasp of his other hand on the sponge (on the brass ball), can modify the strength of the application without disturbing his apparatus. The wet sponge on which he presses with the other hand, acts, as we have seen, like a hydro rheostat." In practice the current was increased until it was "pleasantly painful" for the patient. Comment was made that repeated use of this technique had little effect on the therapist; although if many treatments are given the therapist might be weary at day's end.

General faradism included slow movement of the hand, (or sponge) over the head, face and neck, lateral and dorsal. When the hand, (or sponge) passed over the back of the patient's head, Beard and Rockwell (1891) stated, "The current is felt through the ramifications of the occipital nerves, giving rise offtimes to sensations not only painless but absolutely agreeable."

While progressing over the neck, it was recognized that the current could gain access to the cervical sympathetic and pneumogastric (vagus), as well as the phrenic nerves and the brachial plexuses. At one point on the neck, called the clio-spinal center, all of these nerves were stimulated. Beard and Rockwell (1891) stated, "There is no other single place on the surface of the body where the electrical influence can be communicated to so many important nerves as at the clio-spinal center." They continued, "This application, so far from being painful, is to many positively agreeable. The thrill which it communicates to the nerves is often so delightful that the patient requests to have the application prolonged."

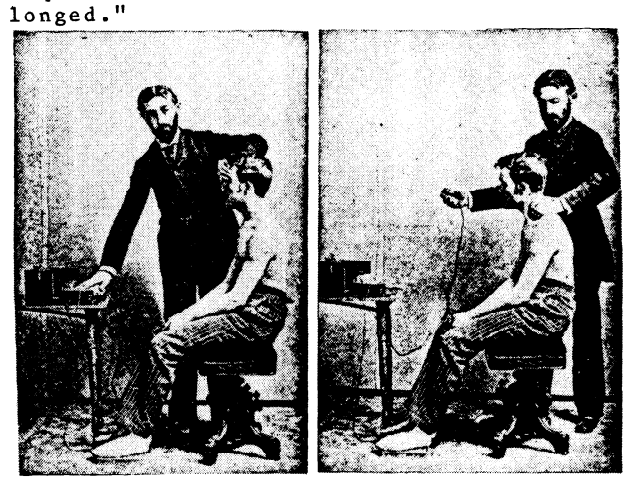


Figure 4-7. The electric-hand technique for applying faradic current in which the therapist is in series with the induction coil and patient (From Beard and Rockwell Medical & Surgical Uses of Electricity. New York 1891, W. Wood Co. 788pp.).

As the electrode was passed downward over the spinal column, a stronger current was needed to obtain a response. As the hand (or sponge) passed the level of the kidneys and spleen, it was moved laterally so that these organs could receive the current. Along the path of the electrode, the superficial muscles contracted tetanically. Beard and Rockwell (1891) reported, "If a strong current be applied over the lower portion of the spine, between the upper border of the ossa innominata, a slight sensation is sometimes, though by no means uniformly, communicated to the rectum and male genetial apparatus, the penis and the testicles, through the spinal nerve supply."

The electric hand (or sponge) was not always passed over the upper extremities. However it was routinely applied to the thorax where tetanic contractions of the superficial muscles were obtained. It was stated that current could not reach the heart because it was so deep in the thorax. The electrode was advanced over the abdomen where current reached the stomach and bowels and finally down the anterior and posterior surfaces of both limbs. Faradization of the genitals was infrequently required as part of the general treatment.

General faradism as just described required about 15 minutes, the least time devoted to the head and most to the spinal column. Typically, two treatments were given each week and a course of therapy consisted of between 15 and 25 treatments.

General faradization was used to treat a wide variety of afflictions, such as dyspepsia, hypochondriasis, nervous exhaustion, hysteria, neuralgia, rheumatism, paralysis, temporary constipation and insomnia. Following the treatment, most patients experienced a feeling of "enlivenment or exhilaration" that lasted several hours. Many felt drowsy and desired to sleep; this response is surprisingly similar to that with the electric air bath. The relief of pain was a common experience. Some felt hungry and a few needed to evacuate the bowel and bladder, and not surprisingly, sometimes during treatment.

A few patients had undesirable responses, such as "temporary undefinable nervousness", weariness and slight muscle pain; these symptoms appeared in a few days. It was well recognized that the type of response depended upon the personality of the patient. Beard and Rockwell (1891) stated that the beneficial tonic effects "are more rapidly appreciated by the active and nervous than by the cold and phlegmatic". What an astute observation!

General faradization really included some local faradization which will now be described. However before doing so, it is useful to observe that general faradization must have been an ecstatic sensory experience which was produced without drugs!

Localized Faradization

The application of faradic current to selected regions of the body paralleled the technique used with static and galvanic current. However unlike these, faradic current produced strong motor and autonomic effects. The rationale offered by Duchenne (1872), although stated awkwardly, is quite clear. Discussing localized faradization he wrote, "At the instant of application of electrodes connected to an induction apparatus (coil) to the cutaneous surface, the natural electricity of the body is decomposed, its poles of opposite polarity are accumulated toward each point in contact with the electrodes, and escape in sufficient quantity to neutralize the current which came to trouble the state of repose." Thus localized faradization was believed to exert a local corrective effect. However, Duchenne believed that it also had a central effect; he wrote "localized faradization mildly excites the nervous centers." This then was the rationale for localized faradization.

Some very remarkable responses were obtained with localized faradization. There was preoccupation with stimulating motor nerves. Accordingly those sites on the body surface where motor nerves were excited most easily were sought. It was Ziemssen (1864) who first charted their locations. Figure 4-8 is one of his charts which identifies what are now called "motor points". Not content to merely locate these points, he went on to discover their anatomic basis. Using fresh cadavers he first located many motor points, marked them and later dissected the underlying tissue to discover that these points are over regions where a nerve enters a muscle.

Using these motor points, local faradization was practiced widely. Some of the indications for its use were peripheral and reflex paralysis and neuralgia. Less obvious was its use for effusions, sprains, local injuries, amenorrhea, diminished sperm production and atony of the bowel and bladder. In the latter two applications the bowel and bladder were evacuated prior to insertion of the electrode. Surprisingly, the goal was not to promote a contraction for evacuation; rather it was to treat the muscle fibers.

The sensory organs were also faradized with the exception of the eye. Faradization with an ear-canal electrode, a nasal electrode and a sublingual electrode were not uncommon for impairment of the respective sensory system. Some of the autonomic nerves were also treated: the vagus was stimulated with electrodes on the neck or in the esophagus. The cervical sympathetic nerve was stimulated with skin-surface electrodes. However these treatments were controversial.

Electrodes

A remarkable variety of electrodes was used. For local faradization, the textbooks of medical electricity of the latter part of the nineteenth century abound with illustrations. Figure 4-9 illustrates typical examples. All electrodes established contact with the moistened skin and the amount of sensation varied considerably, being dependent on the electrode size, (small electrodes were painful), the site of application (the face, rectum and scrotum being very sensitive), and the type of induction coil, as pointed out by Duchenne (1872). We now know that shocks from coils with a large inductance produced the most painful shocks because the pulse duration is longer.

Respiratory Resuscitation

In the mid and latter part of the nineteenth century respiratory arrest due to chloroform anesthesia and coal-gas fumes was by no means uncommon. At this time, faradization was a popular treatment and it was logical to apply it to produce a respiratory effort by stimulating the phrenic nerves or the intercostal muscles.

Ziemssen (1857, 64) appears to have been the first to use electrophrenic faradic stimulation with skin-surface electrodes. The following translation from his paper is due to Althaus 1873:

"A servant-girl, aged 27, was found in her bed early one morning, axphyxiated by charcoal fumes. Counter-irritation of the skin proved unavailing in inducing respiration; (and when Ziemssen was called in,) the pulse and respiration were almost imperceptible; the skin was getting pale, the temperature of the extremities low,

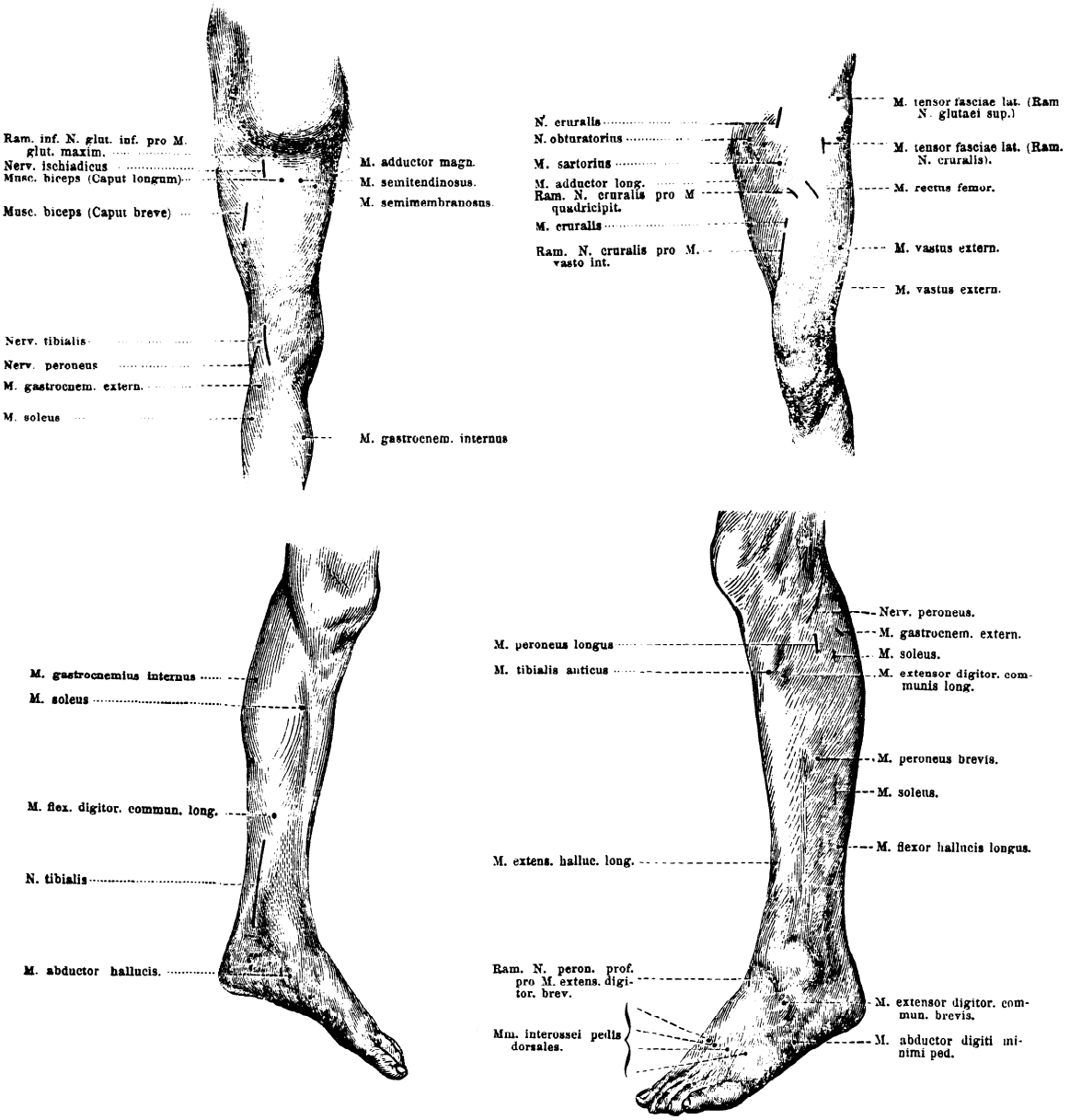


Figure 4-8. Continued.

after death." Beard and Rockwell also included a chapter on the technique in their book "Medical and Surgical Uses of Electricity" (1891). In chapter 35 they recommended that 1) large well moistened sponge electrodes be applied over "the external borders of the outer borders of the sterno-cleido mastoid muscles at the lower end of the scaleni muscles". . ."In some cases it is sufficient to put one respiratory arrest associated with ventricular defibrillation.

Cardiac Pacemaking

It is very tempting to view the electrical resuscitation efforts of the nineteenth century with some enthusiasm in the light of our modern knowledge of cardiorespiratory resuscitation. However certain basic physiologic facts must be recognized. The galvanic resuscitations, in which a battery was connected intermittently to neck and thoracic electrodes could indeed produce a twitch in the respiratory muscles and a single ventricular contraction. With this technique the hazard was minimal and the potential for success was high, as described in the chapter dealing with galvanic therapy. However, when faradic current was applied to electrodes in the same location, the situation is vastly different. Although the respiratory muscles could be tetanized to produce a strong inspiratory effort, the effect of such current on the ventricles is fibrillation. This fact had been known since 1850 when Hoffa and Ludwig demonstrated it in the dog. Moreover, McWilliam (1887) had shown that once started in warm-blooded animals larger than the cat, rabbit, hedgehog, etc., it did not stop spontaneously. Despite these facts, clinicians repeatedly described faradization of the heart with chest electrodes. It is not possible to discover the number of catastrophic incidents that occurred.

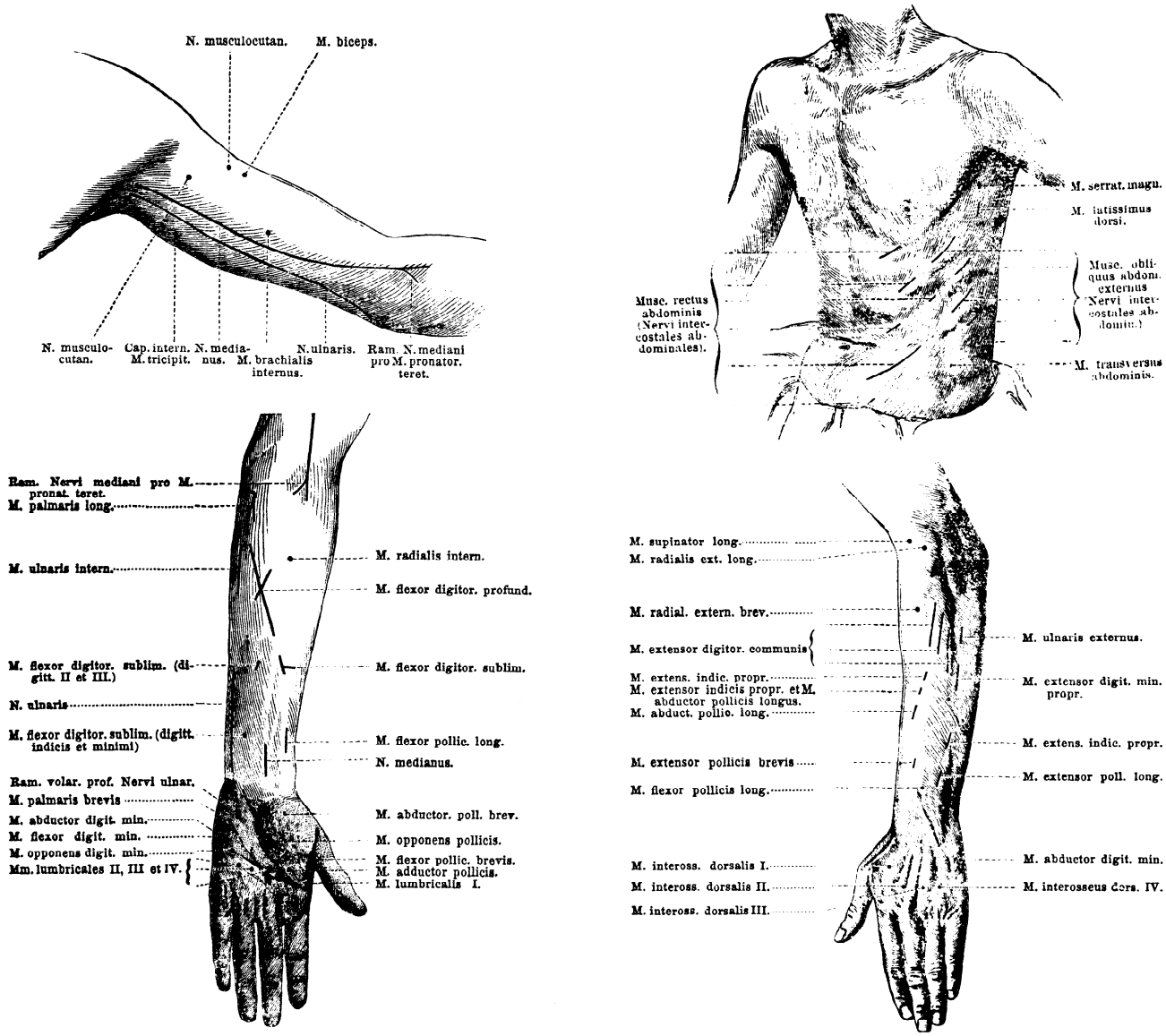


Figure 4-8. One of the first motor-point charts indicating skin-surface sites where the lowest intensity stimulus could produce a motor response. (From Ziemssen, H. Die Electricitat in der Medizin. Berlin 1864. Von August Buchwald. 169pp.).

and the rales in the trachea more marked. The phrenic nerves were now rhythmically faradized. When the chest was seen to expand, the girl began to cough, the cheeks showed a faint flush, and the extremities became warmer. Faradisation was continued, with short interruptions, for two hours, when respiration was fairly re-established. Eleven hours afterwards respiration was regular, and the patient was quite well the next day."

In the second edition of his book, Ziemssen (1864) reported further studies with electrophrenic respiration in cases of asphyxiation due to carburetted hydrogen gas, charcoal fumes and freezing after alcoholic intoxication and respiratory arrest due to chloroform. Friedberg (1859) resuscitated a four-year old boy who experienced respiratory arrest due to chloroform. One electrode was placed on the neck and the other on the seventh intercostal space. Hardie (1871) reported successful electrophrenic respiration in a 10-year old boy who had stopped breathing due to chloroform anesthesia. A second case reported by Hardie was a 42-year old woman who experienced respiratory arrest due to chloroform. Transchest electrodes and rhythmic application of faradic current produced respiratory movements and the color improved, the pupils contracted and soon spontaneous respiration was restored.

Despite occasional failures, rhythmic faradic phrenic-nerve stimulation with skin-surface electrodes gained considerable popularity. Duchenne (1872) devoted substantial space to it in his book "De L'Electrisation Localisee". Preferring transcervical electrodes he wrote "Artificial respiration produced by electric contraction of the diaphragm develops considerable movement of air; increases the vertical diameter of the thorax and the inferior half of its transverse diameter. Moreover electric excitation of the phrenic nerves, which provide contraction of the diaphragm, can also provide noisy respiration in the cadaver, some time

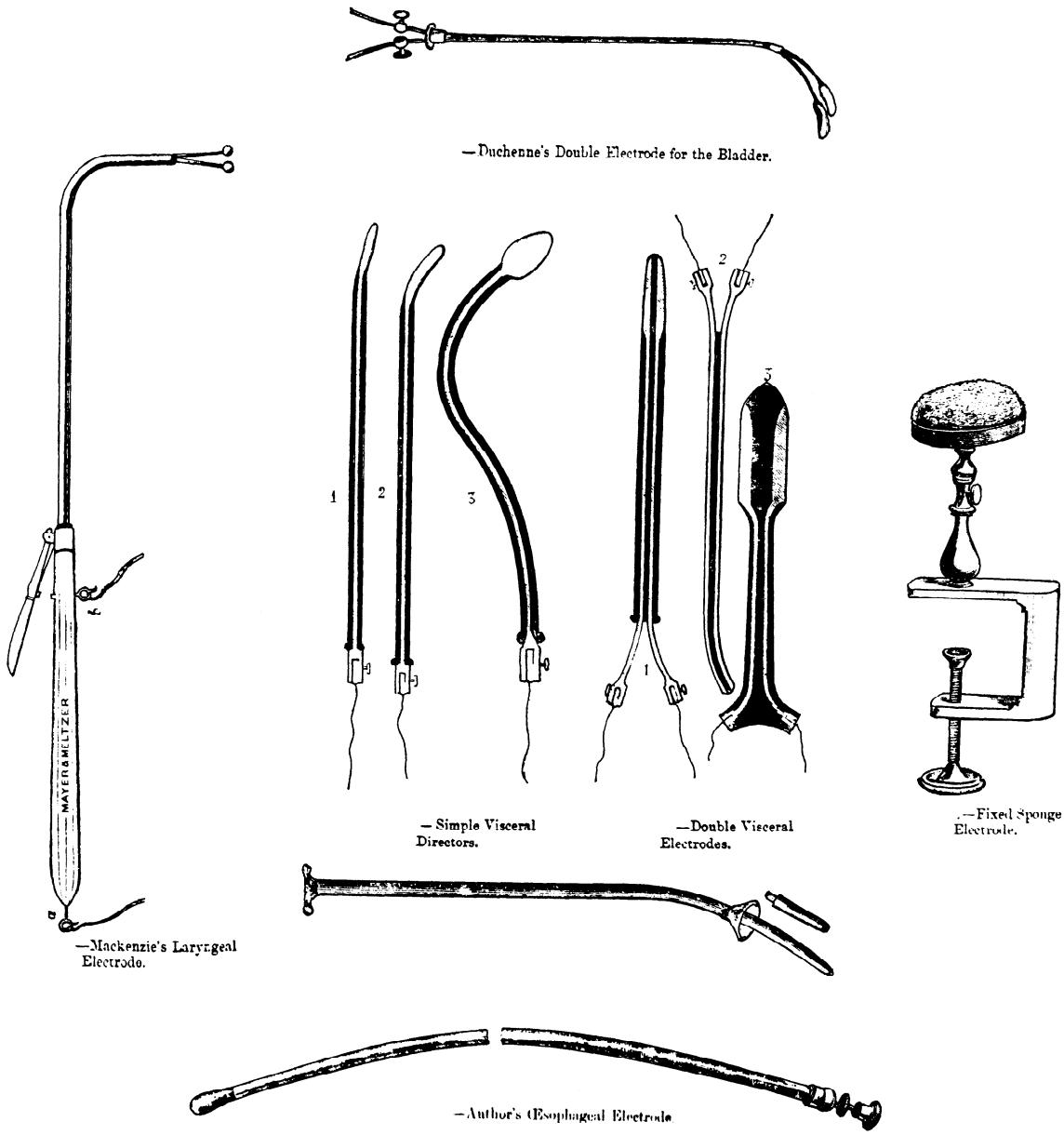


Figure 4-9. Various electrodes for applying faradic current. (From Althaus 1873).

During the latter part of the nineteenth century, sudden and unexpected death was frequently encountered. Respiratory and cardiac arrest were a common recurrence with chloroform, the favorite anesthetic of that day. The first to start speculating about these facts was McWilliam (1889) who distinguished between syncope with and without survival. He postulated that in the former case, the heart's action was inhibited, largely by vagal action and in the second, by ventricular fibrillation. He pointed out that the hypoxia resulting from the former could lead to the latter - a fact that he demonstrated in open-chest dogs.

McWilliam (1889) realized that with vagal cardiac inhibition, rhythmic stimulation delivered to the ventricles, would produce a contraction and a flow of blood from the heart. After having demonstrated the correctness of his thesis in dogs, he then postulated the use of what we now call cardiac pacemaking in man. He wrote:

"We want a much more effective and speedy mode of exciting rhythmic contraction, and one that will have a direct and powerful influence in calling forth a series of beats in the depressed or inhibited heart, while at the same time free from the danger of throwing the ventricles into delirium (fibrillation). Such a mode of excitation seems to be available in the form of a periodic series of single induction shocks sent through the heart at approximately the normal rate electrode over the phrenic nerve and the other over the seventh intercostal space, 2) Bursts of faradic current applied three times per minute , 3) an assistant should press down firmly on the abdomen to assist expiration."

Indications for use of rhythmic electrophrenic stimulation given by Beard and Rockwell (1891) were respiratory arrest from opium poisoning, asphyxiation, drowning, and carbonic acid gas poisoning. They also called attention to the fact

that there have been failures with rhythmic phrenic faradization. They wrote, "It is useless to expect good results if five minutes have elapsed since life appeared extinct." In citing the complications they wrote, "A medical acquaintance informs us that an attempt of this kind (faradization to produce inspiration), which he made in a case of opium poisoning proved instantaneously fatal in the patient. Under ordinary methods, the patient was recovering, but in order to expedite the progress, faradization was tried. One pole was placed on the ribs and the other somewhere on the neck in order to find the phrenic nerve. Immediately the patient ceased to breathe and no further treatment availed to resuscitate her".

The fatal result just described was likely due to ventricular fibrillation. The fact that one electrode was probably near the cardiac apex, the duration of the pulse of faradic current was in the order of a msec or so and the current intensity was high, favors cardiac excitation. The use of a much shorter duration pulse, which would still stimulate a motor nerve like the phrenic, and the use of a slightly different precordial electrode location, could have probably averted this fatality. However, at that time, the strength-duration curve had not been discovered, although ventricular fibrillation by direct cardiac stimulation had been produced by Hoffa and Ludwig (1850). By the 1920's phrenic nerve stimulation had been abandoned, evidence of which comes from a lack of its inclusion in Jones' textbook of Medical Electricity (1920).

The frequent respiratory arrest that accompanied chloroform anesthesia and the successful use of phrenic faradization led Hardie (1871) to recommend that every practitioner make a faradic apparatus "the invariable accompaniment of the chloroform bottle."

As it stands now, neither the optimum location for skin-surface electrodes, nor the optimum pulse duration for maximum phrenic nerve stimulation and minimal cardiac effects are known. Careful studies of these factors constitute a promising area for future research. The fact that the respiratory nerves and muscles retain their ability to respond vigorously for a long time after circulatory arrest argues in favor of reinvestigation of this technique to provide artificial respiration in an emergency situation such as the of cardiac action. A single induction shock readily causes a beat in an inhibited heart, and a regular series of induction shocks (for example, sixty or seventy per minute) gives a regular series of heartbeats at the same rate. Never on any occasion have I seen fibrillar contraction excited by such a mode of stimulation. In order to elucidate more fully the influence of a series of induction shocks upon the inhibited heart, I have frequently (in the dog, cat, and rabbit) performed such experiments as the following. The animal being chloroformed, and means being taken to preserve, as far as possible, the normal temperature, the thorax and pericardial sac were laid open; artificial respiration was kept up through a cannula introduced into the trachea. The heart was inhibited by stimulation of the vagus nerve in the neck, and then a periodic series of induction shocks (regulated by a metronome) was applied to the apex of the ventricles. Contraction of the auricles and ventricles was recorded by an adaptation of the graphic method: a blood-pressure tracing was simultaneously made in the usual manner. In this way I was able to obtain an accurate record of the various changes, while at the same time some further information was obtained by direct inspection of the heart. A series of single induction shocks excites a corresponding series of cardiac beats; the ventricular contraction precedes the auricular contraction when the exciting shocks are applied to the ventricles. Each systole causes the ejection of a considerable amount of blood into the aorta and pulmonary artery, and a marked rise of the blood-pressure at each beat. The mean pressure is raised from the low point to which it had fallen in consequence of the cardiac standstill; it does not, however, attain the normal height, even though a long series of beats is elicited by the stimulating shocks. This fact is due to the feebleness of the auricular contraction under inhibitory influence. For the auricles beat so feebly (in response to the stimulation) that they are unable to pump their contents into the ventricles in the normal vigorous fashion. The ventricles fill very slowly, and at the moment of contraction, contain much less blood than in the normal state; hence the amount of blood thrown into the aorta in a given space of time is much diminished, and the arterial pressure fails to attain its ordinary height. Nevertheless, the artificially excited beats are decidedly advantageous, inasmuch as they arrest the fall of the blood-pressure and even cause a rise--involving an improvement in the circulatory flow in the coronary system, as well as in the other vessels."

McWilliam continued with his observations on the response to pacing as follows:

"But when a regular series of stimuli is employed, the contraction power becomes rapidly improved; the beats increase in force, and often approach the normal strength. Similarly, when the heart has been greatly slowed by inhibitory impulses, the spontaneous beats are frequently reduced in energy; but the application of a periodic series of induction shocks (at approximately the normal rate) leads not only to the manifestation of a regular series of beats at the same rate, but, as a rule, to a pronounced augmentation in the force of the individual beats.

"Hence it is evident that, in addition to the improvement of the blood-pressure resulting from direct excitation of the heart by a series of induction shocks, there is also a beneficial effect exercised upon the contractile mechanisms

of the inhibited heart. The depressing influence exerted through the vagus nerve upon the rhythm and contraction force are in large measure counteracted by direct excitation of the organ."

Aware of the fact that with ventricular pacing, the atrial contribution of filling is lost, he proposed pacing the atria and ventricles simultaneously; he obviously missed the subtle point relating to the A-V conduction time. Nevertheless, his concept, in a way, anticipated double pacing. He wrote:

"In order that such excitation should be as effective as possible it is probably best to send the stimulating shocks through the whole heart, so that the auricles may come directly under their influence as well as the ventricles. In order to do this in man, one electrode should be applied in front over the area of cardiac impulse, and the other over the region of the fourth dorsal vertebra behind, so that the induction shocks may traverse the organ. The electrodes should be of considerable extent (for example, large sponge electrodes), and they and the skin should be well moistened with salt solution. The shocks employed should be strong, sufficient to excite powerful contraction in the voluntary muscle.

"Such a method, it seems to me, is the only rational and effective one for stimulating by direct means the action of a heart which has been suddenly enfeebled or arrested in diastole by causes of a temporary and transient character. Of course, at the same time the expedient of artificial respiration must by no means be neglected, but, on the contrary, most sedulously attended to."

McWilliam's thoughts on ventricular pacemaking in man were, unfortunately, unheeded until 1932 when Hyman built the first cardiac pacemaker and used it clinically. Even this demonstration went unheeded until 1952 when Zoll performed his life-saving studies with closed-chest pacing in patients with Stokes-Adams disease.

Ventricular Defibrillation

Modern ventricular defibrillation dates from the work of Kouwenhoven and his associates, who in the early 1930's started to use 60-Hz alternating current to defibrillate canine hearts with directly applied electrodes. The fact that ventricular fibrillation was a lethal cardiac arrhythmia was known since Hoffa and Ludwig produced it by applying faradic (induction-coil) current to the canine ventricles. In the latter part of the 19th century, there was much interest in the effect of electric current on the heart. In addition to d'Arsonval, many started investigation of this phenomenon. Among these were Prevost and Battelli who reported studies in 1899 on the effect of direct current, capacitor-discharge current and alternating current. Experimenting with different current intensities they were able to produce respiratory arrest and ventricular fibrillation with body- surface electrodes. They found that low-voltage shocks produced ventricular fibrillation, but high- voltage shocks did not. They wrote:

"In a previous note (18 March 1899) we have shown that the fibrillary tremulations produced in the dog, in which they are definitely established, can under certain conditions be arrested, the heart re-establishes its beats, if one submits the animal to passage of a current of high voltage (of 4800 volts, for example)." They continued "Whatever be the cause that provoked the fibrillary tremulations of the heart, in the dog or in the adult cat, they can be abolished and replaced by true rhythmic contractions, with restoration of arterial pressure if one applies to the heart an electric discharge (not too weak, not too strong), if one does not allow a lapse of time more than about 15 seconds." Clearly they had made a discovery that was later to impact medicine.

It is interesting to note that Kouwenhoven and his associates ultimately discovered the Prevost and Battelli papers which had been available for more than three decades, as had ventricular fibrillation as a clinical entity, often being a complication of chloroform anesthesia. However, there were few clinical electrocardiographs until the 1920's and without them ventricular fibrillation would have been difficult to diagnose. The discovery of Prevost and Battelli, in no way, diminishes the important contributions of Kouwenhoven and his colleagues who gave us both direct-heart defibrillation and closed-chest cardiac compression.

Perspective

Faradic stimulation became extremely popular as a therapeutic technique in the late 1800's. However, its use did not persist - even for respiratory resuscitation. Although Sarnoff and his colleagues revived it in 1948 and 1950, it never regained its position as a resuscitative procedure in treating sudden respiratory arrest. Interestingly, Ziemssen's motor points became useful for a short time in the hands of Ritchie (1944) who showed that the chronaxie was long following peripheral nerve injury and shortened as reinnervation proceeded. Unfortunately, electromyography came on the scene at the same time and Ritchie's technique never gained popularity.

Perhaps the most surprising event relative to the history of faradic stimulation is the lack of follow-up on the study by McWilliam, who clearly demonstrated the efficacy of cardiac pacing in the arrested dog heart. He even proposed closed-chest pacing in man and stated where the electrodes should be placed to stimulate both the atria and ventricles using single induction shocks. What is surprising to the author is that there was an urgent clinical need at that time because sudden pulselessness was a common event during the induction of anesthesia.

Chapter 5. High-Frequency Current, Diathermy and Electrosurgery

Introduction

High-frequency current was applied to living tissue to achieve bulk heating; this technique became known as diathermy. It was also applied to a small area electrode on or over tissue to produce localized heating; this application embraces the field of electrosurgery. However, before these applications could arise, it was necessary to know the physiological response to high-frequency current.

Physiological Response

Toward the end of the nineteenth century, considerable interest was focused on choice of the best type of electric current as a source of electrical energy. Edison favored and pioneered the use of direct current; Tesla was the champion of alternating current. There naturally arose the need to know the physiological effects of direct and alternating current. Because of the extremely low power loss associated with long-distance transmission of alternating current at high voltage, interest in direct current distribution faded quickly. Unquestionably the leader in research on the physiological effects of alternating current was Arsenne d'Arsonval, physician at the College of France. He published numerous papers (1893, 94, 97) on this subject and the following material was derived from them.

In his studies of the importance of frequency, d'Arsonval immediately encountered the problem of generating alternating current having a wide frequency range. There were alternators that could provide current of 20 to a few 100 Hz. To extend the range, d'Arsonval obtained a special Gramme alternator that produced current up to 10,000 Hz.; but he needed generators for lower and higher frequencies. For the former he contrived (1891, 94) a most ingenious device which displayed the voltage curve and the force of contraction of a frog nerve-muscle preparation on a smoked-drum kymograph. Figure 5-1 shows his instrument which consisted of a vertical cylinderical electrolytic potentiometer of copper sulfate. The ends of the electrolytic column were connected to a 10-volt battery (P). The positive end of the potentiometer was connected, via a direct-current blocking capacitor C, to an indifferent electrode on the muscle (M) and to ground T (terre). Into the cylinder dipped a copper wire (P'), insulated everywhere except at the tip. The copper wire was mounted on a lever (L) which was caused to move up and down in the electrolyte by a motor-driven cam (E); the other end of the lever identified the position of the potentiometer wire by scratching soot from a kymograph drum (F). The force of muscular contraction was also recorded by another lever (L') which was applied to the kymograph drum. The nerve (N) was connected to the moving potentiometer wire by wire A. As the cam (E) rotated, the voltage applied to the nerve-muscle preparation varied sinusoidally. The amplitude of the voltage depended upon the eccentricity of the cam and the number of cells connected to the electrolytic potenteometer. The frequency of the stimulating voltage was equal to the number of revolutions per second of the cam. By using this instrument, along with various alternators and the Gramme machine, d'Arsonval was able to show that the muscular response decreased with increasing frequency of electric current.

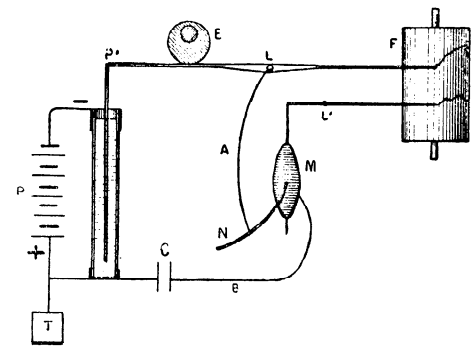


Figure 5-1. d'Arsonval's method of generating low-frequency sinusoidal alternating current, recording its voltae waveform and muscular response on a smoked-drum kymograph (F). (From d'Arsonval. 1891 C. R. Acad. Sci. and Cours d'Appel 1894).

d'Arsonval (1892, 93, 94, 97) extended his studies to determine the effect of very high-frequency current on the body. The landmark experiment that he conducted is shown in Figure 5-2. He employed a Hertz oscillator, consisting of two Leyden jars (B) and an air-core coil (C-C'), the ends of which were connected to a series circuit consisting of a 100-watt light bulb (L) and two human volunteers (D). When high voltage was applied to the positive (+) and negative (-) terminals of the spark gap, an arc was struck and the coil and Leyden jars (capacitors) formed an oscillating circuit, delivering an alternating current with a frequency of about 500,000 Hz. (cycles per second) through the two subjects (D) and the light bulb (L) which glowed brilliantly. At this point the current flowing through the subjects was about 1 ampere. d'Arsonval stated that with three amperes, a disagreeable sensation of heat is encountered. (Imagine the difficulty in securing approval for these studies from modern human subjects use committees).

Clearly, d'Arsonval had shown that high-frequency current, when delivered to the body by conductive electrodes, did not produce contractions in skeletal muscle; nor did it stimulate sensory receptors. Thus the stage was set for the controlled application of high-frequency alternating current to heat living tissue (diathermy) and when applied to a point electrode, to develop high local heating capable of producing tissue dessication, coagulation and

cutting, the three functions provided by the electrosurgical instrument.

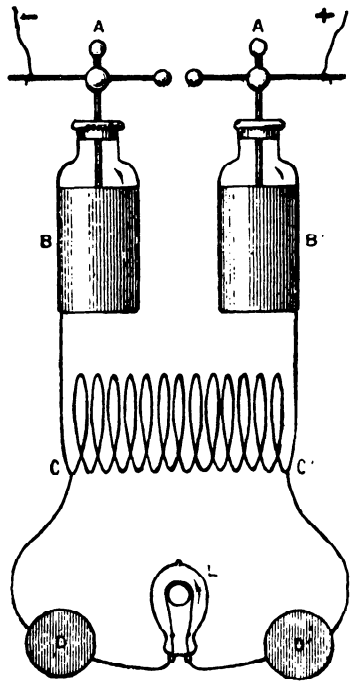


Figure 5-2. d'Arsonval's apparatus for passing one ampere of high-frequency current through two subjects (D) in series with a 100-watt lamp (L), connected to a Hertz spark-gap oscillator. (From d'Arsonval, A. Arch. Physiol. 1893, 5:401-408.)

d'Arsonval proceeded to show that substantial current could be passed through the body by capacitive coupling. Figure 5-3 illustrates a subject on a chaise longue with an electrode below the cushion connected to the (vertical) coil of the high-frequency oscillator; the other end of the coil was connected to an electrode in the subject's hand. d'Arsonval stated that more than 300 mA can be passed through the subject with this method. The name used for the chaise longue became the "condensing couch". Later, when capacitive coupling was used, the term "condensation" was sometimes used.

Inductive heating was also demonstrated by d'Arsonval. Figure 5-4 illustrates a rabbit and a man inside long solenoids through which high-frequency current flowed. d'Arsonval stated that with the inductive method, no metallic contact is made with the subject. Moreover, the current induced in the subject was not confined to the surface of the body. From this and the previous study, d'Arsonval anticipated medical diathermy.

d'Arsonval also commented on the sensation perceived from sparks due to high-frequency current. He stated that although minimal sensation was perceived with his radiofrequency coil, one that produced a higher frequency, current, e.g. 20-30 MHz, would possibly elicit no sensation. The observation that sparks from a high-frequency current did not stimulate paved the way for electrosurgery.

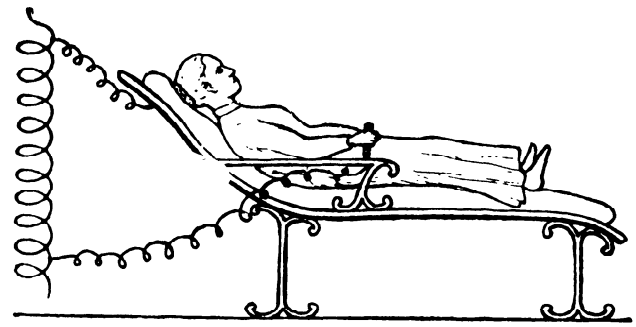


Figure 5-3. The condensing couch, showing d'Arsonval's method of capacitive coupling via the large electrode below the mattress. (From L'Oeuvre Scientifique de Prof. d'Arsonval. Doin & Cie., Paris).

Therapeutic Applications

Long-Wave Diathermy

d'Arsonval's first experiments were conducted with electrodes which made electrolytic contact with the body. The frequency he used (500 kHZ) corresponds to 600 meters, which is designated a long wavelength. Soon physicians began to use frequencies of 1 MHz and higher to produce therapeutic heat. One of these was Doyen (1917), a surgeon, who reported that he used a spark-gap radiofrequency generator (1 MHz) connected to electrodes to warm hypertensive patients prior to surgery to lower the blood pressure and thereby reduce bleeding.

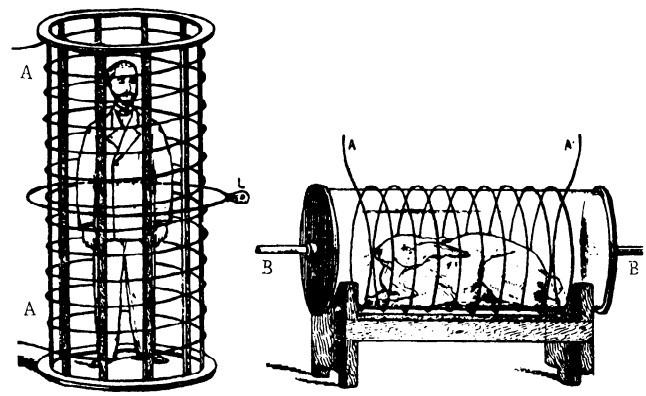


Figure 5-4. Inductive heating of a man and rabbit described by d'Arsonval. (From Action de l'electricite sur les êtres vivants. 1894 Cours d'Appel, Paris).

The pioneer of long-wave diathermy was Nagelschmidt (1907, 28), who originated the term. In 1928 he presented an excellent review of the methods used at that time. Electrodes were placed directly on the skin using saline to provide a low-impedance contact. Special electrodes were designed for the urethra, vagina and rectum. Circular skin-surface electrodes, 2, 4 and 9 cm in diameter, and rectangular electrodes 4 x 6, 5 x 12 and 10 x 20 cm were also popular. With the smaller electrodes, a fraction of an ampere was used. With the larger electrodes, one ampere or more was employed. Interestingly enough, Nagelschmidt's report showed smoked-drum hymograph records of the pulse during passage of the diathermy current. Surely this was one of the earliest patient-monitoring efforts.

Long-wave diathermy was used to treat a wide variety of ailments. Elevated temperature (fever therapy) was popular at that time, as was the use of heat to relieve pain originating from a variety of causes. There were also numerous inappropriate applications of long-wave diathermy. Complications were by no means absent; skin burns and arcing under the electrodes were not uncommon if the electrodes were poorly applied. Such radiofrequency burns are painful, often deep and slow to heal. It is therefore not surprisingly that when a non-contract method of radiofrequency heating, namely short-wave diathermy, became available, the popularity of long-wave diathermy diminished rapidly.

Short-Wave Diathermy

It was the development of power vacuum tubes in the pioneering days of radio during the early 1920s, that permitted the generation of sufficient high-frequency power to produce tissue heating. It would appear that it was Stiebock (1935) who developed the earliest high-frequency (88 MHz) short-wave diathermy using electrodes in direct contact with the skin. The use of skin-contact electrodes with this high-frequency generator provided little advantage over the lower-frequency instruments; nonetheless, heating with short-wave power had been demonstrated.

A considerable step forward was made by Schereschewsky (1926, 33) when he showed that heating could be produced by capacitive coupling. Using frequencies ranging from 8.3 to 130 MHz (36 to 2.3 meters), he heated a mouse in a celluloid box with electrodes placed outside the box.

Short-wave diathermy started in Europe around 1925, according to Stiebock (1935) who referred to his own studies in Vienna. He reviewed the literature, cited Schereschewsky's research and provided the first indications for the use of short-wave diathermy. He advocated its use for intermittent claudication, gangrene of the foot, carbuncle of the upper lip, and eczema. Partial success was encountered in treating otosclerosis. However, it was Schliephake who championed the cause for short-wave (20 meter) diathermy using capacitive electrodes. His book "Les Ondes Electriques Courtes en Biologie" published in Paris in 1938, contains a wealth of information on the technique which employed electrodes covered by glass chambers, later called glass boots. He stated that he became convinced of the benefits of short-wave diathermy when he successfully removed a furuncle from his own nose, although no details of the treatment were given.

Another book published at about the same time "Short-Wave Diathermy" was presented by de Cholnoky (1937) and outlined the proper applications for a variety of capacitive electrodes. In addition to the glass-chamber electrodes, special flexible conformable insulated electrodes were described for the nose, forehead and breast. He also discussed inductothermy (the use of a coil to induce heating) and recommended proper electrode application to avoid creating hot spots on the skin.

There was controversy over the mechanism of the therapeutic benefit by short-wave diathermy. Some believed that the beneficial effect was due to heat; others suggested that there was a non-thermal effect. It was soon recognized that enhanced blood flow played an important role. A remarkable photograph showing vasodilation produced by short-wave diathermy was presented by de Cholnoky (1937). Figure 5-5 is a reproduction of his illustration of the swimming membrane of the frog before (a) and after (b) treatment with diathermy. The remarkable thermal vasodilation is beautifully evident.

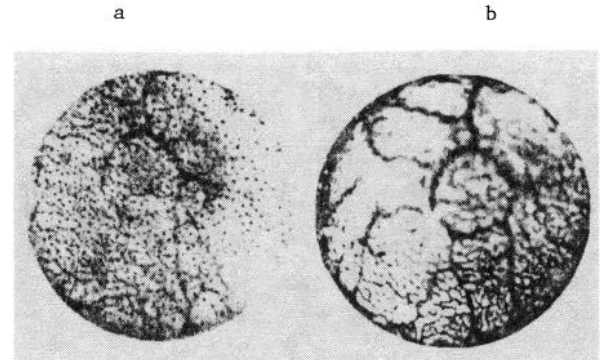


Figure 5-5. Vasodilation in the swimming membrane of a frog.
a - before short-wave treatment
b - after short-wave treatment
(From de Cholnoky, T. Short-Wae Diathermy, New York, 1937. Columbia University Press, p. 60, (310 pp.).

de Cholnoky provided an interesting account on the rapid acceptance of diathermy. He stated that "there have been up to 1937, well over 750 articles in the current literature, and 18 books on the subject." Short-wave diathermy was off and running a race that continues today.

An interesting event in the history of diathermy relates to its use to elevate body temperature. Electropyrexia was the name given to the method of raising whole-body temperature with short-wave diathermy. In the early part of this century, fever therapy was a popular curative procedure. Patients were placed in hot cabinets, baths of hot paraffin and sometimes injected with micro-organisms that raised the body temperature. When the thermal capabilities of short-wave diathermy were recognized, special body-heating cabinets were built in which only the head protruded. Along the sides of the cabinet were large metal electrodes. The patient was wrapped in toweling to absorb the perspiration and prevent arcing to the electrodes. The literature of those days reports that as much as five pounds of perspiration can be shed during one treatment. It was not uncommon to raise body temperatures to 106.7°F and maintain it at this level for 5 1/4 hours (Neymann et al 1932). Such fever-therapeutic measures did cure a variety of ailments, but there was no explanation for the successes and failures that occurred.

There is another little recognized event in the history of short-wave diathermy that is worthy of description. The event relates to the use of short-wave diathermy to devitalize malignant tumors. This evolution probably derived from recognition of the fact that radiofrequency current is a form of radiant energy and the X-ray, another form of radiant energy, was used to treat malignant tumors. To test the effect of radiofrequency (68 MHz) current; Schereschewsky (1933) implanted tumor cells in the bellies of mice and rats. When the tumors reached 5-10 mm in diameter (in about 5 days), they were treated using a specially constructed insulated electrodes with the current being applied for 5 to 15 minutes. One to four treatments were administered. Almost without exception the tumors regressed and about 25% of the animals survived; the remaining 75% succumbed to intercurrent disease after the tumors had receded. Schereschewsky attributed these successes to tumor heating and used thermocouples to measure tumor temperatures which ranged from 48 to 49.6°C. Histological examination of the tumor sites revealed extensive coagulation necrosis, indicating that the blood supply to the tumor had been dramatically reduced. It is noteworthy that the adjacent normal tissue was much les affected.

Remarkable as these results were, they could not be duplicated by de Cholnoky who used 66 to 100 MHz radiofrequency current applied to electrodes 5 to 10 cm from the body. Rats were used and highly malignant rat sarcoma and Flexner carcinoma were innoculated into the belly. After treatment, in only 2 out of 25 animals did the tumors regress.

de Cholnoky's study (1937) probably attenuated enthusiasm for the case of radiofrequency current to treat malignant tumors. However, interest in tumor heating was revived in the mid 1970's, and is presently experiencing the type of careful research that was difficult to carry out in the mid 1930's. There is now ample proof that some tumor types are devitalized when heated with radiofrequency current. However, the tumoricidal mechanism is unknown. It is postulated that the difference in blood vessels and difference in blood flow to normal and adjacent tumor tissues results in differential tumor heating. The higher blood flow to normal tissue, due to thermally induced vasodilation, acts as a coolant, thereby allowing the tumor to become hotter.

Vacuum-Tube Electrodes

Several localized diathermy techniques employed capacitive electrodes made of glass and containing air at low pressure. These devices, often called vacuum electrodes, vacuum-tube electrodes or luminous electrodes, produced radiation, e.g. visible light, heat, ultraviolet or soft x-rays, depending on the pressure within the glass envelope and the applied voltage. Such electrodes were applied to the body surface or in a body opening. Figure 5-6 illustrates typical examples. The electrodes shown in Figure 5-6A,B were passed over the scalp, face, or other superficial regions. Figure 5-6C illustrates the rectal, D the urethral and E the vaginal electrode. A set of such electrodes came in a velvet-lined, polished wooden case with a contoured well for each electrode. A universal connector in a handle accepted any of these electrodes and allowed connection to be made with one terminal of the diathermy machine. The return path for the current was via a hand-held or dispersive electrode placed on the body. When the patient could lay on the condensing couch, the large electrode therein provided the return path for the current.

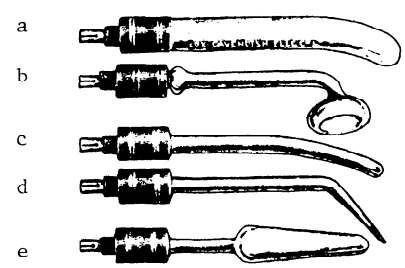


Figure 5-6. Vacuum electrodes: body-surface tubes (a,b), rectal tube (c) urethral tube (d) and vaginal tube (e). (From Essentials of Medical Electricity. Cumberbatch, E. P. London 1939. Henry Kimpton. 528pp).

When a typical electrode of the type shown in Figure 5-6 was placed on the body, or in an opening in it, and the diathermy was activated, the electrode emitted visible light; the color of which, depended on the degree of vacuum in the electrode. According to Eberhart (1916), the pressure in vacuum electrodes ranged from one thousandth to one millionth atmosphere. With a low vacuum, the glow was reddish. Decreasing the pressure caused the color to become blue, violet, and at about one ten thousandth atmosphere, the color becomes whitish; with a higher vacuum, the radiation becomes invisible. Thus, with a low vacuum, mainly visible light is emitted; with a higher vacuum, ultraviolet rays are produced. When an extremely high vacuum was used, it is believed that soft x-rays were produced. Thus the properties of these electrodes depended on their internal pressure, as well as the type of gas therein and the applied voltage.

It is noteworthy that when many types of vacuum electrode were passed just above the surface of the skin, there occurred a faint, but characteristic crackling sound. It was believed that ozone and oxides of nitrogen were produced by this technique. In addition, the skin was heated; therefore the electrode had to be moved continuously. Cumberbatch (1939) stated that the procedure stimulates secretion from the sebaceous glands and this secretion condenses on the glass, leaving an oily film which must be removed after the treatment. If the electrode emitted ultraviolet rays, ozone was created; therefore the electrode would have germicidal properties.

When the appropriate vacuum electrodes shown in Figure 5-6 were placed in a body opening, the tissue where the electrode emerged became exceedingly warm, indicating a nonuniform distribution of current along the length of the electrode. This fact could be demonstrated by placing the thumb and forefinger on the active electrode. At the point of contact, and in the region of the tube toward the connection to the diathermy, the glow was brilliant. Beyond this point, there was little, if any, glow. To minimize this effect, a platinum wire electrode was run the length of the tube within it. Another technique for defining the location of the glow discharge consisted of configuring the glow chamber and placing it within an outer glass sleeve, as shown in Figure 5-7. The basic design of these "insulated electrodes" consisted of an enlarged glow chamber communicating with a much smaller diameter tube which communicated with another large diameter chamber. The latter provided communication with the diathermy when placed in the universal electrode handle. Over these three components was a glass tube of uniform diameter, and contoured for the purpose of the electrode. When activated, the large and small diameter tubes glowed; however, the current was distributed to the tissue mainly by the large diameter glow chamber within the body opening.

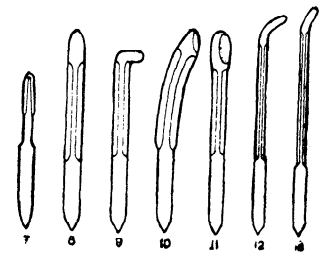


Figure 5-7. Various types of "insulated" vacuum electrodes in which the glowing chamber was connected to the electrode section (lower larger chamber) via a capillary tube to ensure that the glow occurs mainly in the active part of the electrode. (From Eberhart, N. M. High Frequency Currents. Chicago, New Medicine Publ. 320pp).

Indications For Use

There were many uses for vacuum electrodes. However, not all practitioners recognized the different properties of the different types of electrode. Although most therapists had a full range of electrode shapes, few had the different types in each shape. By far, the most popular was the medium-vacuum electrode which emitted "an agreeable purplish glow" as many textbooks stated. In accounts of the various therapies, it was not always stated which type (e.g. high or low vacuum) was used.

The body tube was moved above the surface of the scalp to treat alopecia, and over the skin to treat herpes zoster, neuritis, psoriasis and acne vulgaris. In the latter case, the ultraviolet light and ozone are obviously beneficial. The same electrode was used for the pain of gout and rheumatism. The vaginal electrode was applied for menstrual pain and vaginal discharge. The vaginal and urethral electrodes were used in cases of discharge due to infection. The rectal and aural electrodes were used for the same purpose.

Non-Vacuum Electrodes

It was realized that the vacuum electrode became hotter than desirable. In addition, the nonuniformity of current distribution described earlier, caused concern. Accordingly a series of non-vacuum (capacitive) electrodes was developed. They were essentially the same in contour as the vacuum types, except that instead of gas, the interior of the tube was silvered and air at atmosphere pressure was contained therein. Thus, no glow was emitted. According to Cumberbatch (1939) these electrodes provided a more uniform current distribution and

operated cooler than the vacuum electrodes. The indications for use of the non-vacuum electrodes were the same as for the vacuum electrodes.

Finally, it was soon realized that it was necessary to know the temperature of an electrode introduced into a body cavity. Some nonvacuum electrodes contained a thermometer. Probably because glass was fragile, the hollow metal electrode, containing a thermometer was developed. Sometimes the electrode was insulated with a rubber sleeve; other times it was not. The former was a capacitive electrode and the latter was a conductive electrode. It was clearly stated in most electrotherapy texts that temperature is more important than the current setting and that the patient's response is more important than both.

Microwave Diathermy

The use of microwaves for tissue heating had to await the availability of radiofrequency generators capable of delivering about 100 watts continuously. Krusen (1947) of the Mayo Clinic reported on his early interest in microwave heating around 1937 when he consulted Lee DeForest, inventor of the triode vacuum tube. However, technology was not available for this requirement. Generators of centimeter-wavelength radiofrequency current were being developed at the Bell Telephone Laboratories. At this time (1938), these magnetron generators were only capable of producing a few watts of continuous power. Later in that year, the klystron was developed which offered the promise of more power. Krusen had followed these developments closely and made serious attempts to obtain these devices. Unfortunately, World War 2 (1939-45) had begun and these devices became classified, being destined for radar.

Following the war, Krusen found a cavity magentron capable of producing 400 watts at 3000 MHz at the Massachusetts Institute of Technology. By June 1946, he had obtained one of these devices through the courtesy of the Raytheon Co. It then became possible to create a suitable microwave generator and use it to evaluate the capability of microwaves to heat living tissue.

The first tissue microwave heating studies were conducted by Dr. Leden, fellow in Physical Medicine, working with Dr. Krusen. The 3000 MHz (10 cm) energy was directed into dog limbs using a hemispherical radiator, 3.5 inches in diameter, placed 5 cm above the skin. About 65 watts were applied for 20 minutes. Using needle thermocouples, the temperature was measured at two depths before and after application of the microwave energy. It was well known to Leden that it was not possible to obtain accurate temperatures if the thermocouples were in the microwave field. With the thermal dose of 65 watts for 20 minutes, a temperature rise of 3 to 5^{o}C was produced.

This presentation will not describe the subsequent microwave tissue heating studies. The important point, however, is that a new method of tissue heating had been introduced in which the radiofrequency energy could be directed at the tissue with a radiator or antenna. The technique is in use at present.

Electrosurgery

In electrosurgical procedures, high-frequency alternating current flows through living tissue to produce dessication, coagulation or cutting. These three effects depend on the current intensity, the type of active electrode and the technique used. In the U.K. the term surgical diathermy is the name for the technique. The term electrocautery is sometimes incorrectly used to designate electrosurgery; by definition an electrocautery is an electrically heated instrument for performing surgery. An important distinction is that with the electrocautery no current flows through the tissue.

Ever since d'Arsonval demonstrated that high-frequency alternating current did not stimulate nerves and muscles, the opportunity was at hand to make practical use of this phenomenon. As described in the previous section, it was quickly put to use to heat living tissue with large-area electrodes. Its value in producing a highly localized thermal effect was soon recognized and studies were commenced in Europe and the USA to exploit this phenomenon.

Just before the turn of the twentieth century, the race was on to develop bigger and better induction coils, i.e. ones that could produce longer and thicker sparks of higher frequency current. Thus the Ruhmkorff, Oudin and Tesla coils were widely available, as was the Hertzian spark-gap oscillator. With any of the high-frequency coils it was customary to draw sparks from an electrode held over the skin to destroy superficial blemishes. According to Doyen (1909), Pozzi named this technique fulguration (fulger=lightning). No return-path electrode was used; the capacitance of the subject to ground provided the return path for the current. Doyen carried out histological studies and discovered that the tissue damage did not extend beyond 3-5 mm below the skin surface. Because he wanted to destroy malignant tumors at a greater depth, he investigated methods of attaining this goal. After some preliminary studies he wrote:

"I noticed also that, to obtain stronger effects, it was necessary to join the metallic wire on which the subject reposed to one of the extremities of the oscillating self-induction circuit, meanwhile the active electrode is connected to the other extremity. This electrode is maintained a little distance from the patient (bipolar voltaisation) or similarly one can put it in contact with him (the patient), the spark is found to

be suppressed (electrocoagulation). But one obtains, particularly by elongating the electrode, muscular contractions, so violent that this method is almost inapplicable in certain regions, at the end of the vaginal cul-de-sac and the neck of the uterus."

Doyen then stated that the muscular contractions were diminished by using a Oudin coil, which delivered a higher frequency current. He went on to use his electrosurgical generator, treating malignant superficial tumors to a depth of 4 to 5 cm.

Certain points should be noted in Doyen's paper; for example, he found that he needed a return-path electrode (the wire mattress on which the patient lay). He introduced coagulation by placing the electrode in contact with the tissue and he introduced the bipolar technique. Moreover, he carried out temperature studies on the tissues surrounding the active electrode. Although he did not have fine control of the current intensity, his control was such that he recommended the technique for the removal of malignant tumors in the esophagus and larynx. Eight years later (1917) he published the first textbook on electrosurgery, "Surgical Therapeutics and Operative Techniques" which was translated into English by H.S. Browne.

Unaware of the European research, William L. Clark, of Philadelphia, was conducting experiments leading to the development of electrosurgery. Clark presented his initial results at the American Electro-Therapeutic Association meeting in Saratoga Springs, New York, on September 14, 1910. In his classic (1911) paper, Clark clearly described the need for high power and its fine control. He used a high-voltage electrostatic generator to excite a spark gap and its associated oscillating circuit. There are no better words to describe the study than those of Clark who wrote "A static machine of large output was procured. A 5 H.P. motor was used to drive 12 revolving plates of special construction for strength and durability, capable of 2,000 revolutions per minute giving about twenty times the output of the ordinary static machine. By varying the size of Leyden jars used as resonators, all thermic degrees were obtained, from hyperemia to cauterization." (Figure 5-8 is the author's concept of Clark's equipment). "I experimented with my own hand for the milder effects, and with an ordinary cake of soap for higher degrees of heat. A balance was struck when it was possible to dessicate a piece of soap through a piece of paper without charring or discoloring the paper, and by extracting the plug of soap and crushing it between the fingers it was pulverized. The soap immediately surrounding the dessicated areas was very wet, as it could not evaporate on account of the paper, and condensed on the soap. When no paper was used, small droplets condensed upon the surface of a small mirror held in close proximity. It was found that the same effect was obtained with raw liver and potato. This seemed good proof that the exact degree of heat for dessication was attained, which could be sustained without increasing the degree and without danger of burning. Small warts and moles were next successfully treated, after which I became more pretentious and cautiously applied it to epithelioma, exuberant granulations, cutaneous pigmentations, hemorrhoids, tattoo marks, acne pustules, X-ray keratosis, lupus and one case of bladder papilloma, aided by the catheterizing cystoscope. Its applicability in various other conditions will suggest itself. By slightly increasing the intensity of the current and bringing the metal point in closer contact, a destructive effect may be produced through fluids, as is necessary in the case of tumor of the bladder."

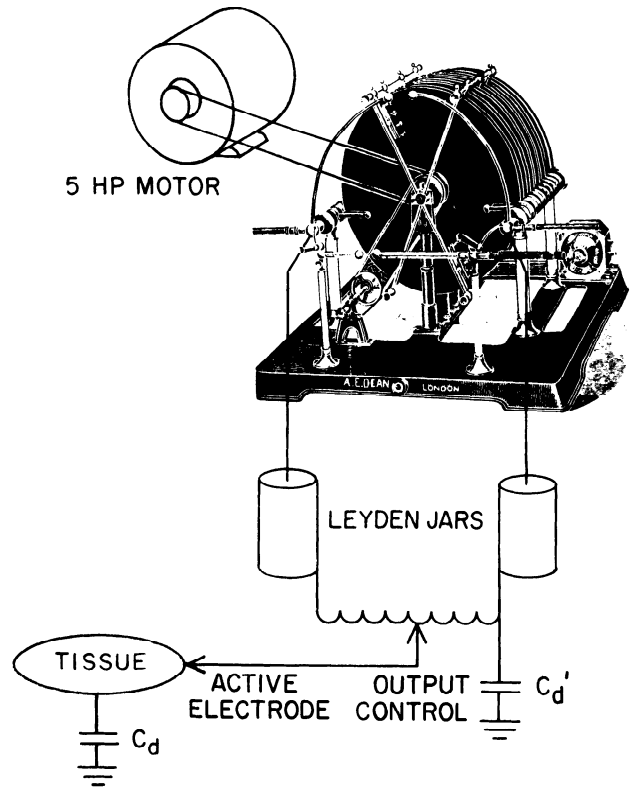


Figure 5-8. Author's cocept of Clark's electrosurgical instrument, comprising a 12-disk electrostatic machine and a spark-gap oscillator, consisting of a coil and Leyden jars and an active electrode. No dispersive electrode was used, the return-path for the current being by C_d and C_d', the distributed capacitance ground.

Clark stated that the radiofrequency current sterilized the incision, deadened the nerve endings and sealed small bleeders. He then recounted his experience with 317 lesions in 78 patients in which he treated "15 epitheliomas, 2 lipomas, 12 pigmentations, 3 granulating ulcerations, 12 hemorrhoids, 4 tattoo

marks, 10 acne, 58 X-ray keratosis, 4 chancroids, 10 condyloma, 1 bladder papilloma, 4 lupus lesions, 60 moles and 122 verruca".

The team that really promoted and popularized use of electrosurgical techniques consisted of Cushing and Bovie, the latter being a physicist who was attached to the Harvard Cancer Commission. Bovie had developed an electrosurgical unit for excising carcinomas. According to Fulton (1946), Cushing became aware of Bovie's work in the spring or summer of 1926 and contacted him. Together they developed a dual electrosurgical unit, one part providing cutting current and the other generating coagulating current. They then developed the loop, ball and point electrodes, each of which could be mounted in a sterilisable handle. Harvey Cushing then used the dual-purpose Bovie unit (which operated at 1-3 MHz) to remove brain tumors with so little bleeding that he called back many of his previously inoperable patients for surgery. In 1928 he published his results and shortly thereafter interested the Leibel-Flarsheim Co. in duplicating the device for commercial sale.

Before Cushing was pioneering the use of radiofrequency current in neurosurgery, Ward (1925) had developed a unique method of arresting bleeding in small vessels. His discovery is best told in his own words:

"While I was thus engaged following a radical amputation of the breast, the electrode happened to touch the (blood-vessel) clamp itself and caused a spark at the point of contact. This gave me the idea of running the current down the clamp and in this way concentrating it more directly on the bleeding vessel and on it alone. I tried it out and at once noted a neater area of electrocoagulation and less injury to the surrounding tissues than by the previous technique. This therefore appears to me to be an ideal method of hemostasis, except for large vessels".

Ward then proceeded to describe the technique that he recommended, which is illustrated in Figure 5-9. He wrote:

"The operator grasps the clamp on the vessel in his left hand and holds it at right angles to the surface and clear of all contact with the body except at the tip where the vessel is caught. With the right hand, the active electrode (needle) touches the hemostat at any convenient point and remains a fraction of a second or longer when a small ring of electrocoagulation forms at the end of the instrument, which is now removed. There is no bleeding, and the small area of coagulation is soon absorbed without slough or hemorrhage."

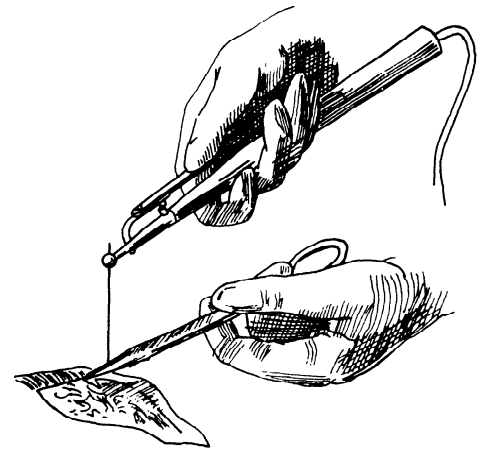


Figure 5-9. Ward's method of applying current to a hemostat to control bleeding in small vessels (Redrawn from Ward, B. E. Med. Journ. & Record 1925, 121:470).

Electrosurgical Instruments

Although the first spark-gap electrosurgical units performed satisfactorily, interest arose in using the vacuum tube to generate the high-frequency current. According to Kelly and Ward (1932), DeForest's new vacuum tube was used to generate radiofrequency current and used to cut dog skin by Neil and Steinberger. However, nothing seemed to come of this effort. Credit for use of the vacuum tube to generate electrosurgical current appears to be due to Wyeth (1924). The narrow-band radiofrequency current exhibited little penetration in the tissue and hence was excellent for cutting; but it exhibited poor coagulating characteristics. Therefore the incision tended to bleed more than with the spark-gap current. According to Kelly and Ward (1932), the vacuum-tube units were so expensive that manufacturers turned their attention to perfecting spark-gap units with adjustable gaps. Empirically it was found that with a wide separation of the spark gaps and with large values of inductance and capacitance in the resonant circuit, the train of 120 Hz damped sine waves was excellent for coagulation. It was also found that the use of lower values of inductance and capacitance (which increased the frequency of the current) and closer spacing between the contacts of the spark gap (which decreased the interval between the trains of damped sine waves) produced radiofrequency current which was excellent for cutting (Groff, 1929). Such an arrangement constituted the design of all spark-gap electrosurgical units, many of which are still in use.

Ultimately vacuum-tube, continuous-wave (unmodulated) radiofrequency current electrosurgical instruments were developed. It was soon found that such unmodulated radiofrequency current provided excellent cutting, but poor coagulation. Apparently, the first to recognize the unique qualities of the spark-gap current (damped sine waves) to coagulate and the vacuum tube (single frequency) current to cut was Groff (1929), who developed a hybrid electrosurgical unit which provided both types of current. According to Kelly and Ward (1932), Groff used his electro-surgical unit with success for many years.

Dispersive Electrode

No dispersive (return-path) electrode was used with many of the first electrosurgical instruments. The return path for the current was provided by the capacitive coupling between the subject and ground. With this arrangement, there is a high probability of skin burns by accidental contact between the patient and ground. The first dispersive electrode was described by Iredell et al (1919) in the U.K. They used a bare metal plate, about 3 in. by 1.5 in., pressed against the patient's skin by the nurse. When the electrode became warm, the current was turned off and the electrode was moved to another site. Mitchell and Lumb (1919, 62), also in the U.K., reported that a typical dispersive electrode of that time measured 6 X 9 inches. They recommended 9 sq. in. of electrode area for every 100 watts of electrosurgical power. They suggested that a soft lead plate, covered by a towel soaked in saline, was an effective dispersive electrode.

Perspective

By 1930 the advantages of electrosurgery were well recognized. Among these are the saving of time, the assurance of asepsis, the absence of bleeding and elimination of transferring infection from diseased to normal tissue (as was common with a scalpel). Wound healing with electrodissection was almost the same as with scalpel cuts. These features were testified to by a panel of eminent surgeons who were convened on the occasion of the Conference on Electrosurgery at the Clinical Congress of the American College of Surgeons (1931). The enthusiasm in these reports, which cover a wide range of surgical procedures, makes for stimulating reading and shows how quickly surgeons embraced the new techniques. At this conference there was only one report on wound healing in which Ellis showed that, except for skin incisions, there is little difference between scalpel and electrosurgical cutting. Shortly thereafter, the first American textbook on electrosurgery was published by Kelly and Ward (1932); in it there is a good review of the histologic changes in tissue in response to electrosurgical currents.

Chapter 6. Quantifiable Stimulators and the Law of Excitation

Introduction

The physiologic and therapeutic uses of electric current described in the preceeding chapters were performed with little understanding of what is needed to stimulate excitable tissue. Knowledge of the nature of the membrane of an excitable cell, and how it is changed by a stimulus is of very recent origin. Even without this information, pysiologists sought to determine experimentally the essential requirements for a stimulus. In this quest they were hampered by the lack of a means to measure stimulus strength and duration. Induction-coil shocks, although convenient, could not be quantitated. After the nature of the capacitor discharge was known, this type of exponentially decaying current could be quantitated, and thus became a candidate for investigative purposes. However, there were those who wanted a single rectangular pulse of current, with a known amplitude and duration, and, despite the lack of measuring instruments, created stimulators that met these true requirements. These stimulators became known as rheotomes, or current slicers. Thus the law of excitation, relating intensity and duration, was discovered empirically using the capacitor discharge (chapter 2) and the rheotome; descriptions of the latter will now be presented, following which there appears an analytical derivation of the strength-duration curve. This chapter concludes with a comparison of the experimentally and analytically derived strength-duration curves.

Rheotomes

Rheotomes, or "current slicers", consisted of mechanically actuated contacts which were used to provide either single or repetitive stimuli of a known duration and frequency. Rheotomes were also used in an ingenious sampling technique to map out the action potential of nerve and cardiac muscle with high accuracy, long before rapidly responding graphic recorders were available. The method involved delivering repetitive stimuli via a fixed pair of contacts around the perimeter of a rotating wheel. A second pair of contacts allowed sampling the action potential for a brief instant at a specified time after the stimulus was delivered. A slow speed, but sensitive, galvanometer averaged the potential at the particular instant after the stimulus. The delay for sampling the action potential was controlled by adjustment of the second (measuring) pair of contacts at the periphery of the rotating wheel. How, in the late 1800's, the method was used by Berstein to map out the action potential of nerve, and by Burdon-Sanderson to map out the R and T waves of the ECG, were reported by Hoff and Geddes (1957). How rheotomes were used as stimulators is the subject of this chapter.

Sometime before it was realized that the duration of a capacitor discharge could be controlled by selection of the size of the capacitance (providing the discharge-circuit resistance was known or was constant), it became obvious that a constant current stimulator of known and controllable duration was needed to examine the fundamental nature of the excitability characteristics of tissue such as nerve and muscle. Accordingly, two types of rheotome were developed: the pendulum and the ballistic. In a most ingenious way, a current pulse of known duration and intensity was produced.

Pendulum Rheotome

Around 1850, Helmholtz, renown for his discoveries in physics and physiology, developed the pendulum rheotome. The device consisted of a pendulum with a heavy steel weight. When raised and released, the pendulum opened a first pair of contacts (SC in Figure 6-1) at the bottom of its decent (i.e. where the speed was maximum); then it opened a second pair of contacts (OC) along its path. The first pair constituted a short circuit across the stimulating electrodes. When these contacts opened, current flowed through the electrodes and excitable tissue. The second pair of contacts was in series with the direct-current source and when these opened, current flow ceased. The duration (t) of the current flow was selected by a micrometer which set the distance (d) between the first and second pair of contacts.

The intensity of the stimulus was determined by the voltage of the battery (E), the position of the slider on the potentiometer P, and the resistance R, which was made large with respect to the assumed resistance of the electrode-subject circuit. The stimulus current was e/R.

Convenient as it was, the Helmholtz pendulum rheotome could not provide a current pulse of adequate brevity for many investigators. Accordingly, Lucas (1907) improved it by constructing a pendulum 540 mm long which operated the two pairs of contacts. With his rheotome, a distance of 5 mm along the arc of the pendulum was equivalent to about 1 ms. Lucas' rheotome permitted easy adjustment for a stimulus duration range of 2-20 msec.

Ballistic Rheotome

The ballistic rheotome of Weiss (1901) predated the Lucas pendulum rheotome and was unusual in design and remarkable in performance. Although Weiss did not publish a picture of his instrument, Figure 6-2 was composed by the author from Weiss' description and illustrates that it operated on the principle of cutting wires with a projectile fired from a carbon-dioxide powered carbine. When fired, the projectile cut the first wire (SC) which removed the short circuit from the two stimulating electrodes, thereby allowing current to flow. When the projectile cut the second wire (OC), the current flow was interrupted. Thus by knowing the velocity of the projectile and the distance (d) between the two wires, Weiss could calculate the duration (t) of the current flow. In those days the velocity of a projectile was measured accurately by allowing it to strike and become embedded in a wooden block suspended from the end of a string, thereby creating a ballistic pendulum. By measuring the maximum displacement of the pendulum, it is easy to calculate the velocity of the projectile at impact. Weiss claimed that a stimulus as short as 77 microseconds was easily obtained with his ballistic rheotome.

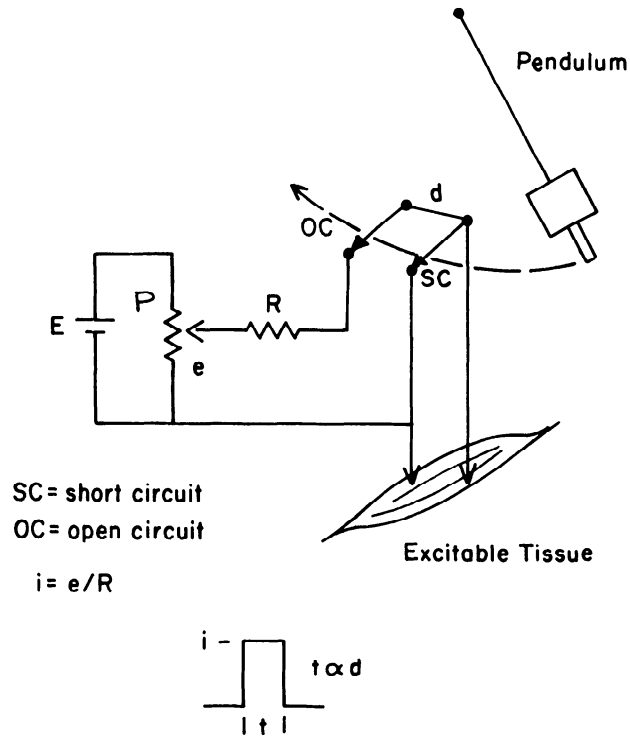


Figure 6-1. The pendulum rheotome. When released, the pendulum opened the first switch (SC), thereby allowing current to flow through the excitable tissue. Then the pendulum opened a second switch (OC) which arrested current flow through the tissue. The duration (t) of current flow depended on the length of the pendulum and the distance (d) between the two switches (SC and OC).

The strength of the stimulus was regulated in the same manner as with the pendulum rheotome. The current (I) that flowed was equal to e/R, where e is the voltage derived from the potentiometer (P) and R is a selected resistance that is many times higher than the assumed resistance of the electrode-subject circuit. Weiss made R=500,000 ohms.

Lapicque (1926) built a Weiss ballistic rheotome for his own use. The projectile was powered with a fulminate capsule. With the contact wires separated about 25

cm, the current pulse was 1 ms in duration.

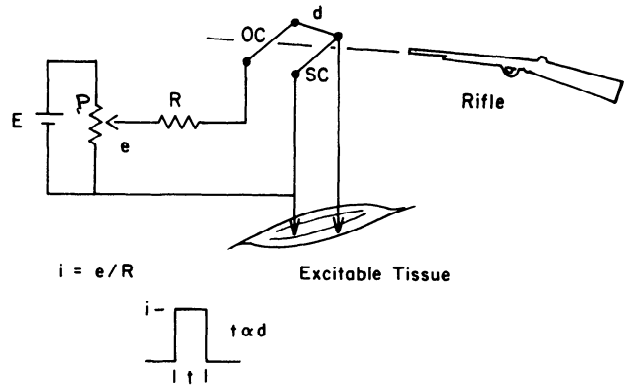


Figure 6-2. The principle employed in the Weiss ballistic rheotome. Current flow is initiated by firing a projectile which cuts the short circuit (SC) wire. Current flow ceases when the projectile cuts the open-circuit (OC) wire. The duration (t) of current flow was dependent on the distance d and the velocity of the projectile, which was measured with a ballistic pendulum.

The rheotome was the stimulator that made it possible for a physiologist to investigate the intimate relationship between the minimum current intensity and duration required for excitation. From the current, voltage and duration, charge and energy could be calculated. Note that the age of electronics was more than a decade in the future. Electronic stimulators with the capabilities of the rheotomes were many decades in the future.

The Law of Excitation

Using mainly the frog nerve-muscle preparation, investigators began to measure the electrical quantities that result in a response. Basically, two types of stimulator were used: the capacitor discharge and the rectangular pulse of current from a rheotome. It is useful to recall that many of these studies were carried out when the ohm, ampere, volt, farad, etc. were being defined by the International Electrical Congress (1881) and consequently the results of the various investigations are difficult to compare. As can be imagined, an enormous amount of work was devoted to discovering the law of excitability using a variety of stimuli. Excellent reviews were presented by Weiss (1901) and Lapicque (1926); both emerged as the leading contenders in the race to identify the law. However, prior to publication of their extensive and intensive studies, it is worth mentioning that it appears to have been Fick (1863) who first discussed the three important attributes of a stimulus; abruptness of onset, intensity and duration, the latter being very important. It was Hoorweg (1892) who carried out a remarkably straightforward series of experiments in which he determined the lowest voltage on different capacitors which, when applied to electrodes on a human subject, would evoke a muscle twitch. He then plotted the voltage (e) versus capacitance (c) as shown in Figure 6-3. Because the peak current is proportional to the voltage, and because the duration of the discharge is proportional to the capacitance (with a constant electrode-subject resistance), Hoorweg had, in reality, published the first strength-duration curve for excitation.

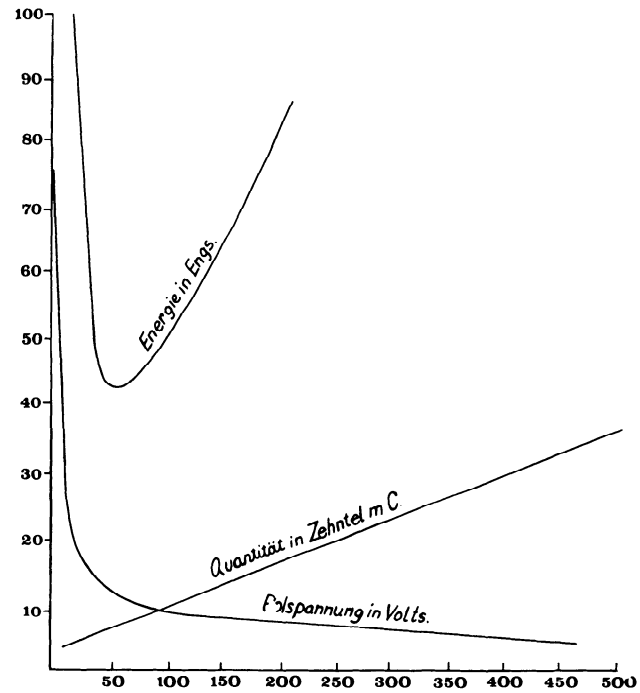


Figure 6-3. The first strength-duration curve obtained by Hoorweg (1892), showing the voltage, charge (quantitat) and energy (ergs) required to stimulate excitable tissue using capacitor-discharge current. The ordinate and abscissa are in relative units, the latter being expressed in capacitance units which are linearly proportional to the stimulus duration (Redrawn from Hoorweg 1892).

Not content with showing only the voltage-capacitance relationship, Hoorweg plotted the delivered energy ($ce^2/2$) versus capacitance which is also shown in Figure 6-3. He clearly demonstrated that there was a capacitance (i.e. duration) for minimum energy. He also calculated what was referred to as the "quantity of electricity", namely charge (q), which is equal to the product of the capacitance and voltage. His plot of the charge versus capacitance is shown in Figure 6-3 by the linear relationship. Had Hoorweg

known that the duration of the discharge was equal to the product of circuit resistance and capacitance, and that the current was linearly proportional to the voltage on the capacitor, he could have scaled the abscissa in milliseconds and the ordinate in milliamperes. Had this occurred, Hoorweg could have laid claim to origination of the strength-duration curve for current, charge and energy. Some time later, the first was attributed to Lapicque (1909) and the second, to Weiss (1901).

Weiss

Weiss, Agrege of the Faculty of Medicine in Paris, and writing in the Italian Archives of Biology (1901), stated that he had experimented with capacitor-discharge current to stimulate nerve and muscle, but disliked the fact that the current decreased during the pulse. He also did not wish to run the risk of small oscillations in current, which was suspected with capacitor discharge, (old suspicions die hard!). To eliminate the problems just described, he devised his ballistic rheotome (Figure 6-2) and then proceeded to determine the relationship between the threshold (constant) current and duration for the excitation of muscle. The current was calculated from the voltage used and the resistance of the electrode-subject circuit, which was made high by the addition of a resistor (500,000 ohms). He thus measured the voltage, calculated the current and charge for each pulse duration and stated: "I calculated the quantity of electricity (charge) and reported it graphically. Also, I saw that the points obtained in the same experiment arranged themselves according to a straight line not passing through the origin, that is to say, in each experiment the quantity of electricity can be represented by the formula q = a + bt, t being the duration of the discharge, a and b two coefficients depending on the arrangement". Weiss went on to state that the coefficients a and b can be calculated by finding the threshold charge delivered using two different durations of stimulus. Figure 6-4A is a linear graphical relationship of Weiss data for the charge required to excite toad, turtle and frog muscle. Figure 6-4B represents the same data on a log-log plot. In the same paper, Weiss showed that the same type of relationship applied for capacitor-discharge current.

It is somewhat surprising that Weiss did not discuss the consequences of his linear charge-duration relationship, namely that the current increased with decreasing stimulus duration; the latter was left for Louis Lapicque to exploit.

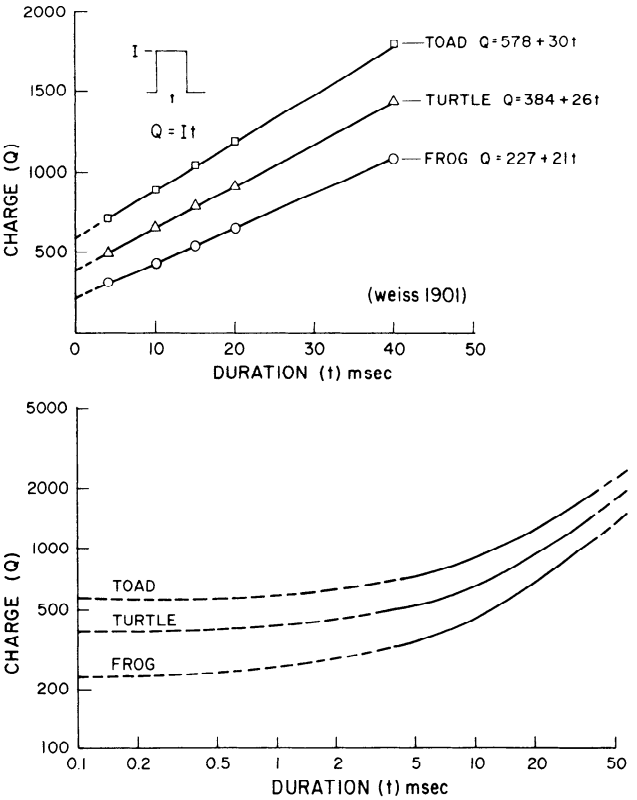


Figure 6-4. Linear (A) and log-log (B) representations for charge versus duration for toad, turtle and frog muscle, plotted from data presented in Weiss' (1901) paper.

The Lapicques

In 1905 Madame Lapicque presented her thesis to the Faculty of Sciences at the University of Paris. In it, she described the Law of Excitation using frog, crab, and aplysia muscle, stimulated with capacitor-discharge current. The empirical expression that she obtained was $v = \frac{k}{c} + br$, where v is the voltage on the capacitor c; r is the circuit resistance, and k and b are constants. Recall that current is voltage (v) divided by resistance (r), and stimulus duration (t) is proportional to the product of capacitance (c) and resistance (r), i.e., t = rc. Therefore, her expression for current would be I = k/rc + b, where rc is the duration of the stimulus, expressed as the time constant. This expression was presented later following research with her husband.

In 1909 her husband, Louis Lapicque, reported his results with the capacitor-discharge stimulator (Figure 2-3). He determined the minimum current required to stimulate a wide variety of excitable tissues using different durations of capacitor discharge. From these studies (1909 and 1926) he developed the familiar expression $I = \frac{a}{t} + b$, where I is the current, t is the duration (time constant), b is the threshold current for an infinitely long duration stimulus, which

he called the rheobase. The constant a, depended on the type of tissue. Figure 6-5A presents graphically the Lapicque strength-duration curve; Figure 6-5B is a log-log presentation of the same expression. Later Lapicque (1926) stated that the expression is also applicable to rectangular current pulses.

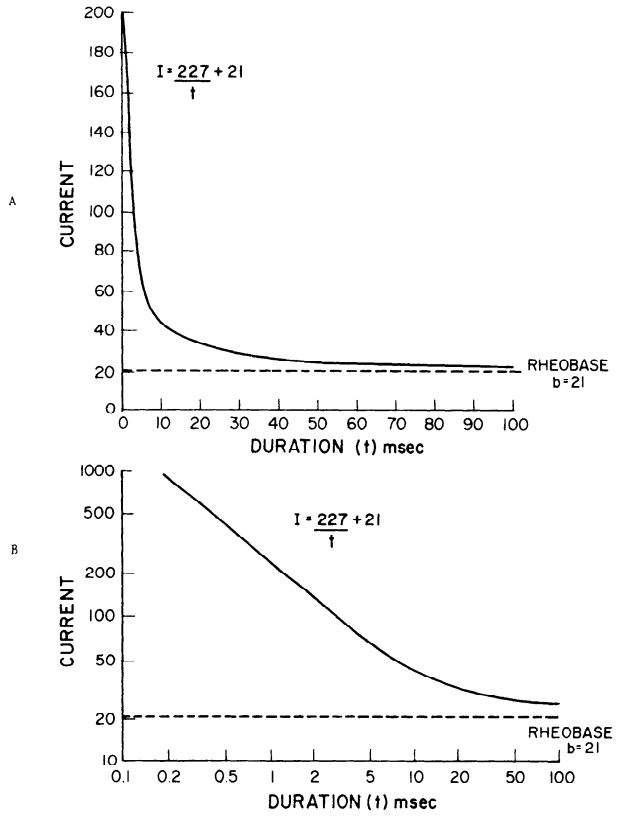


Figure 6-5. The Lapicque strength-duration curve for the current (required to stimulate frog muscle) displayed in linear (A) and log-log co-ordinates (B).

Lapicque (1926) was impressed by the fact that the current-duration curves for different excitable tissues were similar in contour. In fact, he recognized that they differed only in the time axis and rheobasic values. He then scaled his data to the same rheobase and plotted values for different excitable tissues on a log-log scale (Figure 6-6A) to demonstrate clearly that the curves for the different excitable tissues differed only for the duration axis. Recognizing this, he desired to show that the contours of the curves were identical for the widest variety of excitable tissues. To do so, he plotted the excitability curves for the snail (Figure 6-6B) and the spirogyra, a blue-green alga (Figure 6-6C). He then chose a duration corresponding to twice the rheobasic value for each. His statement describing this choice is: "let us apply to each an intensity which is the same multiple (twice for example)". Using this duration, which he called the chronaxie (time value) he scaled the spirogyra excitability curve to that of the snail and plotted the data points together, as shown in Figure 6-6D. When viewed in this way it is clear that the excitability (strength-duration) curves for these widely differing excitable tissues are virtually identical, providing both credibility for the strength-duration curve concept for current and the use of chronaxie as a descriptor for the excitability of irritable tissue. Lapicque then determined the chronaxie values for a wide variety of tissues, showing that the values for the rapidly propagating tissues were much shorter than those for the slowly propagating tissues.

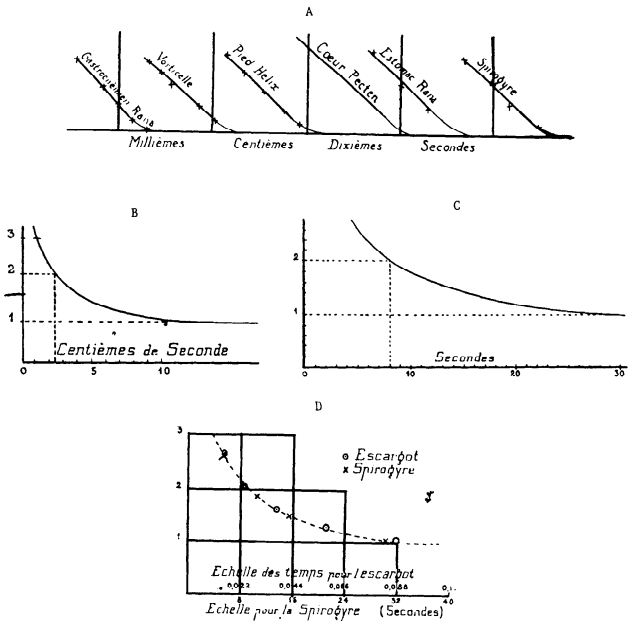


Figure 6-6. Lapicque's method for comparing the strength-duration curves for different excitable tissues scaled to the same rheobase (A). The strength-duration curves for snail and spirogyra are shown in B and C. In D, the data for B and C were scaled using the same chronaxie value to demonstrate that te contours of the strength-duration curves are the same, (From Lapicque 1926).

Weiss and Lapicque

At this point it is useful to bring together the concepts of Weiss and Lapicque to demonstrate that they are merely two manifestations of the same phenomenon. For example, Weiss stated that the charge (q) is linearly related to stimulus duration t as follows:

$$q = a + bt.$$

Now charge is the average current multiplied by the duration. Therefore, division of the Weiss expression by duration (t) gives the following:

$$\frac{q}{t} = I = \frac{a}{t} + b$$

$$I = \frac{a}{t} + b$$

Note that the Weiss and Lapicque relationships merely describe different aspects of the same phenomenon. Both investigators merely described the criteria for excitability differently.

Following directly from the Weiss-Lapicque relationships is the delivered energy (u) which for a rectangular pulse, is equal to the product of the current squared, the stimulus duration t and the resistance (r) of the circuit.

$$u = \left(\frac{a}{t} + b\right)^2 rt$$

Figure 6-7 illustrates the current, charge and energy versus stimulus duration relationships for the empirical Weiss-Lapicque expressions. It is interesting to observe that although Lapicque arbitrarily selected a ratio of twice the rheobasic current to specify chronaxie, this duration has another significance, namely, it is the duration for minimum energy. This fact is easily proven by differentiating the energy expression with respect to duration, equating the result to zero and solving for the duration. To date this fact has not been reported.

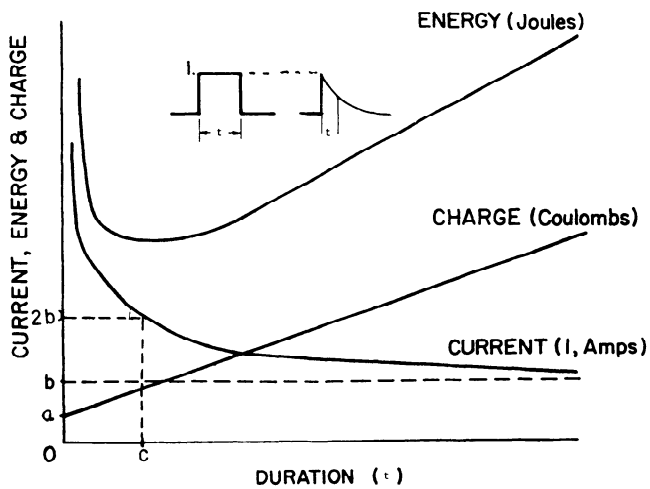


Figure 6-7. The Weiss-Lapicque strength-duration relationships.

Figure 6-7 reminds us that there are three electrical quantities that can be used to describe an electrical stimulus: charge, current, and energy. It is very clear that there is an optimum, but different duration for a minimum for each. Minimum charge occurs with an infinitely short duration stimulus. Minimum (rheobasic) current occurs with an infinitely long duration stimulus. Minimum energy occurs at the chronaxie, the duration corresponding to a stimulus of twice rheobasic strength.

Modern Concept

Elegant and simple as is the Weiss-Lapicque concept for excitability, it is based on curve-fitting from experimentally determined data. There has always been some suspicion that it does not apply over a wide range of current durations. It is now possible to derive a reasonably accurate and useful expression for excitability from the well-known electrical properties of the cell membrane.

Excitable cells are surrounded by membranes that have both capacitance (C) and resistance (R). Excitation occurs when a stimulus reduces the transmembrane potential by a critical amount, ΔV to the threshold potential (TP). Figure 6-8A illustrates diagrammatically the charged resting membrane and its electrical components, R and C. An electrical stimulus (I), consisting of a rectangular current pulse, will divide between the capacitance and resistance, as shown in Figure 6-8B. The sum of the capacitive current (CdV/dt) and resistive current (V/R), results in the first-order differential equation as shown. Pearce et al. (1982) solved this differential equation to obtain the current required for stimulation with pulses of different duration (t) to obtain the following:

$$I = \frac{b}{i - e^{-t/\tau}}$$

where b is the rheobasic current, t is the pulse duration, and τ is the membrane time constant, which is equal to the product of membrane resistance and capacitance, i.e., $\tau = RC$.

Following directly from the expression for current are the expressions for charge (Q) and energy (U). For a rectangular pulse, charge is the product of current and duration; therefore for charge:

$$Q = It = \frac{bt}{1 - e^{-t/\tau}}$$

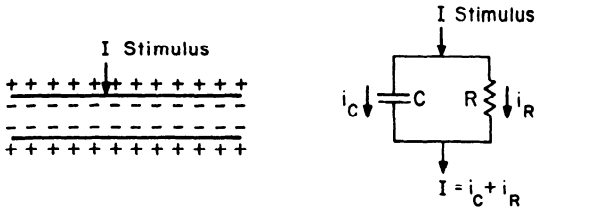
For energy:

$$U = I^2 Rt = \left| \frac{b}{1 - e^{-t/\tau}} \right|^2 Rt$$

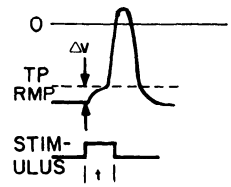
In these expressions, t is the duration of the stimulus, τ is the membrane time constant (RE), and b is the rheobasic current.

Strength-duration curves for current, charge and energy are plotted in Figure 6-9 (solid curves) and reveal characteristics similar to those obtained empirically by Hoorweg, Weiss and Lapicque.

It is now appropriate to compare more closely the analytically derived curves with those predicted by the Weiss-Lapicque expressions. Recall, that Lapicque stated that the value of the constant a in his expression was dependent on tissue type. From the Weiss equation, a is the charge



$$I = i_C + i_R$$
$$= C\frac{dV}{dt} + \frac{V}{R}$$



TP = Threshold potential
RMP = Resting membrane potential
t = Duration

Figure 6-8. The analog of a cell membrane showing its resistive (R) and capacitive (C) components. Excitation results from delivery of a pulse of current of adequate strength to reduce the transmembrane potential by ΔV to the threshold potential (TP).

for a stimulus of infinitely short duration. The analytically derived curve in Figure 6-9 shows that the charge for an infinitely short duration stimulus asymptotes to τb; this can be shown by evaluating $e^{-t/\tau}$ for very short durations. Putting $a = \tau b$ in the Lapicque expression yields

$$I = \frac{\tau b}{t} + b = b(1 + \frac{\tau}{t})$$

Thus the Lapicque expression can be rewritten to incorporate the membrane time-constant, a quantity that is dependent on tissue type. Performing this manipulation permits plotting the Lapicque expression for current in terms of duration in units of t/τ. This has been done and the dashed curve in Figure 6-9 shows that the Lapicque empirical expression for current is not very different from that derived analytically. Similarly the Weiss expression for charge and the expression for energy can be calculated. Figure 6-9 shows these strength-duration curves in normalized form as dashed curves.

There is yet another important point to be made with the Lapicque expression, namely the meaning of chronaxie. Putting $I = 2b$ and duration $t = c$ (the chronaxie), reveals that the chronaxie is the membrane time constant, a remarkable coincidence since Lapicque arbitrarily chose the factor 2b to specify the current for chronaxie. This derivation of course relies on $a = \tau b$, i. e. the short-duration asymptotes for charge are equal for the empirically and analytically derived strength-duration curves.

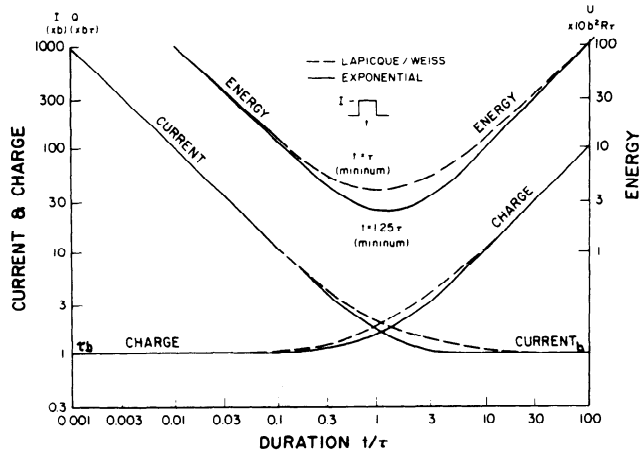


Figure 6-9. Strength-duration curves for current, charge and energy for the exponential expression (solid curves) and for the Weiss-Lapicque expression (dashed curves).

What is most surprising is that Weiss and Lapicque fitted their data to expressions that are not so different than those derived from consideration of the components of the cell membrane which were largely unknown at the time.

Hoorweg, Weiss and Lapicque clearly called our attention to the three different electrical quantities that can be used to describe a stimulus: energy, charge and current. It is important to recognize that there is no single duration for a minimum for all three quantities. Minimum energy occurs with a pulse duration slightly longer than the membrane time constant. Minimum charge occurs with an infinitely short duration stimulus and the charge curve is nearly asymptotic at a duration corresponding to about one tenth of the membrane time constant. Minimum current occurs with an infinitely long duration stimulus; although the current curve is nearly rheobasic for a duration about five times the membrane time constant.

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