PREFATORY CHAPTER

PHYSIOLOGY FROM 1900 TO 1920: INCIDENTS, ACCIDENTS, AND ADVANCES

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This article consists of an attempt to comply in part with the request of the Editor—to interpret on the basis of personal experiences the influences that have aided the development of physiology and channeled advances in the subject during the past fifty years. It was probably assumed that I was qualified for such a task because I entered medical school at practically the beginning of the century, viz., in 1901. As indicated in the title, I have chosen to confine the survey to the first two decades of the century, owing to limitations of time and space and because relative newcomers are perhaps less familiar with conditions prevailing during that period. They may even labor under the delusion that our fund of physiological information was quite meager a half-century ago and that the greatest progress has been made during the past two or three decades. This erroneous belief might excusably be derived from the facts that during the past thirty years the number of physiologists has greatly increased, laboratories have become more commodious and better equipped, enormous funds have become available for the support of research, the number of papers published in more and better journals has skyrocketed, and new discoveries have been announced very frequently, even in lay publications and over the radio.

May I, therefore, assure the present generation that the volume of physiological information that we were required to master as students was by no means small, as can easily be verified by perusal of textbooks such as those of Stewart, 1895 (1); Schäfer, 1898–1900 (2); and An American Textbook of Physiology, edited by Howell in 1901 (3). Candidates for a doctor's degree in physiology might well be required to have a familiarity with the material contained in such texts. A rough estimate of our stock of physiological facts in various periods of the twentieth century can be made rather quickly by comparing the contents of textbooks issued in successive years. A deeper insight can be gained by consultation of outstanding monographs, lectures, and reviews, and, since 1939, of successive volumes of the Annual Review of Physiology. Among textbooks useful for such a survey, the following may be mentioned: Howell, 1905 (4); Nagel 1905–09 (5); Krehl, 1906 (6); Tigerstedt, 1907 (7); Luciani, 1911–21 (8); Starling, 1912 (9); Bayliss, 1914 (10); Hewlett, 1916 (11); Macleod, 1918 (12); Höber, 1919 (13); Burton-Opitz, 1920 (14); Roaf, 1924 (15); Wright, 1926 (16); Bethe, eighteen volumes, 1927–32 (17); Martin & Weymouth, 1928 (18); Halliburton & McDowall, 1930 (19); Winton & Bayliss, 1931 (20); Gellhorn, 1931 (21); Wiggers, 1934 (22); Best &

1 The Past-President's Address at the fall meeting of the American Physiological Society at Columbus, Ohio, September 15, 1950, was based on material in this chapter.
Taylor, 1937 (23); Heilbrunn, 1937 (24); Bard, 1938 (25); Fulton, 1940 (26); Houssay et al., 1945 (27); and Hamilton, 1947 (28). Many of the foregoing have been repeatedly revised, and the dates of only the first issues are indicated. Several equally good texts have probably been inadvertently omitted.

The physiological knowledge available to us in 1900 was a heritage of previous generations. Physiology already owed a great deal to the master mathematicians and physicists of the seventeenth and eighteenth centuries and to the early physiologists who were inspired by John Hunter and Johannes Müller to make functional deductions from the structure of tissues and organs. However, the physiology of 1920 was built largely upon the experimental work of the previous century. Magendie, Legallois, Flourens, the three Weber brothers, von Liebig, Wöhler, Poiseuille, and Bowman were among the more prominent contributors of the first half of that century. Claude Bernard, Ludwig, Helmholtz, and their brilliant pupils, du Bois Reymond, Brücke, Goltz, Brown-Séquard, Kühne, Hoppe-Seyler, Kossel, and many others who worked during the latter half of the nineteenth century, made this a period of most rapid progress through use of experimental methods. Through their genius and zeal the virgin soils yielded bountiful harvests. Indeed, so great had been the crop of discoveries that those of us who entered fields of investigation early in the twentieth century felt that the law of diminishing returns must operate until the soil could be refertilized or until better tools should become available.

The physiological subjects that were most completely understood were those of nerve and muscle, special senses, and circulation; it was therefore natural that these should be more extensively emphasized as disciplines of physiology in medical courses. However, sufficient knowledge concerning functions of the blood; production and flow of lymph; formation and actions of digestive secretions; secretion of milk, urine, and sweat; physiology of respiration and animal heat, had accumulated to fill one of the two large volumes of Schäfer’s textbook (2). While modern neurophysiologists would undoubtedly characterize as “limited” the knowledge of the central nervous system of 1900, it had nevertheless developed to such a degree that many neurologists of today base their diagnoses of nervous diseases essentially on information available at that time. The main ascending and descending tracts of the spinal cord were known, and the effects of lesions involving them had been established. Many characteristics of reflex cord reactions had already been determined by Sherrington through use of mammalian spinal preparations. The effects of various cortical lesions had been investigated experimentally, the motor areas of the cerebral cortex had been mapped in the dog, monkey, and in at least one anthropoid ape. Epilepsy had been induced by strong cortical stimulation, and aphasia assigned to Broca’s area. Despite conflicting opinion regarding cerebellar functions, Sherrington’s summary in Schäfer’s textbook (2, p. 918) has a familiar modern ring: “It (the cerebellum) preponderantly helps to secure coordinate innervation of the skeletal musculature, both for maintenance of attitude and execution of movements.” However, it must be admitted that our knowledge regarding
the functions of the ductless glands and metabolic processes was sadly deficient.

THE FIRST DECADE

I propose now to relate some earlier incidents and accidents that led to my adoption of physiology as a career and to draw such morals and conclusions as seem apropos. Decisions to enter a given profession are not based solely on inborn instincts; somehow, somewhere, sometime, a seed of interest must be planted in fertile soil. If properly nurtured and watered it may sprout into a fervor for the selected vocation; but it can grow into a sturdy plant that blossoms and bears fruit only through continued fertilization, spraying, and pruning. My interest in physiology as a science was not awakened by lectures or reading connected with regularly scheduled courses but through an educational experiment conceived by Lombard in 1902. The experiment consisted in assigning to each group of two students a research problem to be carried out during the last two weeks of a laboratory course. My partner and I were to investigate the debated question, whether the knee jerk is due to reflex excitation or to direct stimulation of the quadriceps maintained in reflex tonus. Of course, little progress was made during the short time available, but, my curiosity having been aroused, permission was given to pursue the quest independently in the evenings and on week ends. A new and simple method for inscribing an isometric contraction of the quadriceps, by the same system that recorded the tap, was devised. The technique is still being used in my laboratory courses for medical students. The results obtained agreed with observations of British physiologists, namely, that, available data being utilized, the interval between the tap and the start of contraction seemed too brief to permit impulses to travel over a reflex path. While these investigations were being pursued, Cushny granted me the privilege of assisting him in his experiments on free afternoons. My duties consisted largely in smoking drums and in cleaning up after the experiments. The stipend was nil, but the recompense for these services was large, for it afforded the opportunity to learn how a great experimenter observes, ponders, and deducts from his observations; for Cushny, as history records, was a pioneer in basic physiology as well as in experimental pharmacology. During this period of immaturity I was already beginning to classify masters of physiology as of two kinds: (a) those like Lombard, who delighted to design new apparatus, maintain the old in prime condition, and test each appliance as to its merits and efficiency, but who failed to make extensive use of such apparatus in experimental work; and (b) those like Cushny, who were content to employ relatively simple equipment, but who were active experimentally and had the vision to formulate research programs of signal value. Since both of these attributes are important, trainees should from the outset endeavor to develop both of these talents equally.

My parasitic association with laboratories of physiology and pharmacology could not help influencing my future inclinations. Lombard's attributes of neatness, precision, and manual dexterity—all had lasting synaptic aftereffects. The opportunity of watching investigators at work proved a
great treat to a young individual. During subsequent years, I have often had opportunities to witness experimental procedures in other laboratories. I have tried to profit from observations of good techniques and equipment and to avoid careless practices and habits noticed in others. Indeed, I have learned to assess scientific reports as much by an investigator’s technical habits as by the actual data and deductions reported on the printed page. As Ludwig stated, “Die Methode ist Alles,” or, as phrased by Flourens, “Tout dans les recherches experimentales, depend de la méthode, car c’est la méthode qui donne les resultats.” The moral to be drawn from my experiences would seem to be that, in order to evoke a research interest in predoctorate or neodoctorate students, one should expose them as much as possible to experimental work in progress within a department. We oldsters prate a great deal about the failure of medical education to provide an adequate number of candidates for careers in basic sciences. At the same time, there seems to be greater insistence upon a medical training as a background for professorial appointment in medical schools. In a measure, we have only ourselves to blame for this lack of interest among medical students. Only exceptionally are medical students urged to witness experiments in progress; all too rarely are those who display some signs of interest invited to help in a minor way. Furthermore, there seems to be an increasing tendency to segregate research and teaching in separate rooms, floors, or divisions; the trend should be rather toward a building arrangement in which the student laboratory can be approached only through research quarters and a departmental library.

To return from this digression, for which I make no apology, I shall relate an even more decisive incident that affected my career. At the beginning of the junior year in medical school (1903) it was my considered plan to engage eventually in the practice of obstetrics and pediatrics. This program was destined to be upset by the resignation of the only instructor in the department of physiology and by the inability to replace him, as a result of which I was practically drafted to accept a half-time post as student assistant. Parenthetically, it is my considered judgment that in 1903 there were fewer physiologists relative to the positions available than at the present time. During this period of student assistantship, which consisted chiefly in aiding in the conduct of laboratory work, time was found to engage in a research on the innervation of the cerebral vessels. A new approach to the problem was found through perfusion of a completely isolated brain, and, when the 18th annual meeting of the American Physiological Society was held at Ann Arbor in December of 1905, it was possible to demonstrate satisfactorily that epinephrine constricts the cerebral vessels. The actual demonstration brought the realization that one can detect an aptitude for research—or its lack—more convincingly by the reactions of a critical audience than by any aptitude test yet designed. If I sensed opinions correctly, I had passed the test. Attendance at the meetings of the American Physiological Society also afforded a grand opportunity for gaining an initial acquaintance with many leading physiologists and for understanding how physiological advances are accomplished. Vivid recollections remain of the demonstration of
heart block by Erlanger, the registration of ventricular volume curves by Y. Henderson, the measurement of renal blood flow by Brodie, and the debate concerning the myogenic or neurogenic origin of the heart beat which ensued after Carlson's paper on the Limulus heart. All of these demonstrations were soon to have far-reaching effects on the interpretation of cardiac and vascular physiology. Younger persons who seem to display an interest in physiological work should be encouraged to attend meetings of this sort and should be assured that the outlay of money required is well invested. In my case it caused the seed of physiological interest to sprout, and the resolution was made to enter physiology as a career provided an opportunity arose. At that time, fellowships of which one could avail himself for entry into basic research were nonexistent. Opportunity arose only through attainment of an academic appointment in which teaching was emphasized and research was regarded as a sort of hobby. Fortunately an instructorship became available in 1906 because Lombard had finally convinced the regents that proper laboratory instruction for 120 students during three fourths of the academic year required an instructor in addition to a professor and two student assistants. Despite a considerable teaching load, I found time for investigations on the innervation of coronary and pulmonary vessels.

The years of my instructorship coincided with a period during which physiology began to challenge the claim of pathology as the foundation of clinical medicine. It was likewise the period of therapeutic nihilism and of faith that most diseases are self-curing through natural compensatory processes. These trends influenced me to become interested in more practical experimental problems, such as the compensatory mechanisms of hemorrhage. I began to appreciate, however, that the pressure recorders available at the time were not adequate to give correct answers to dynamic problems. Optically recording apparatus, such as had recently been designed by Otto Frank, was obviously required. Speculation began to take form as to ways and means by which an experience in the Munich laboratories might be realized, but the answer was not obvious.

During the academic year 1910 to 1911, it was my good fortune that an opportunity arose for gaining executive experience necessary for the conduct of a department. I have since regarded this as a fortunate incident, for the lack of administrative experience may have been contributory to the deflection of promising investigators from research after assumption of professorial duties. A sabbatical leave of absence granted Professor Lombard was the cause of my appointment as acting director of the department. The integration of administrative responsibility, teaching, and investigative work proved quite a thrill. A bold didactic experiment was instituted in which basic physiology was correlated with its clinical application. Such emphasis on the application of physiology to clinical medicine—without sacrifice of basic biochemical, biophysical, and mathematical aspects of the pure science—was developed further after my appointment in Cleveland. A calendar was worked out by which each member of the staff could plan some free time for research in rotation with teaching. At the close of the year an investigation by a member of the staff merited publication. At that time a tradition
or code of ethics had been handed down from Ludwig through his pupils that a department head should not allow his name to be added to a paper by a younger man, even though he might have outlined the work, participated in the experiments, aided in the interpretation of results, and finally, might be largely responsible for the manuscript. I followed this principle then and have continued to do so during my entire career. The current practice of placing the name of a superior as coauthor of a research, especially one in which he has taken little or no part, always appeals to me as useless, unfair, unjustifiable, and, in some instances, selfish.

Unfortunately, success often leads to megalomania. I did not escape it. During the middle of my administrative year confidence grew that I was quite ready to direct a department. Therefore, when two offers of professorships were received, an inflated ego tempted me to accept. In the first case, it was fortunately my privilege to discuss the matter with Dr. Huber, who happened to have Dr. Mall as his guest. Mall, when asked his opinion, replied, "I know nothing whatsoever about you, but, if you are good, the school is not good enough for you; if you are no good, the school is too good for you." Thus, one temptation was avoided. In the second case, I showed to Professor Novy a telegram, offering me a chair in physiology. After a quiet reflection, his answer was, "You are too young to be sitting in a chair; wire back concerning the status of their laboratory stools." I have always been grateful for these sound counsels. I would recommend that young investigators resist acceptance of positions in which advancement is apparent rather than real. The long view should always consider changes only on the basis of opportunity, never solely for the attainment of a better emolument or title. Many a promising career has been wrecked by failure to observe these rules of safety.

The academic year ending in 1911 terminated my fruitful connection with the Department of Physiology at Ann Arbor. Such an association for nearly a decade necessarily served to keep me abreast of the constant advances of that period. It is, therefore, the prerogative of an oldster to recount, and perhaps embellish a bit, the progress that to him seemed important during this decade.

The evolution of new physical principles and techniques and their prompt application to biological problems by Arrhenius, Bayliss, Bohr, Bottazzi, Hamburger, Wo. Ostwald, Jacques Loeb, and others, gave direction and purpose to the study of general physiology. Many of these investigators and others still to enter the field extended their work into the next decade. Thus Loeb, having rounded up his chemodynamic studies in a brilliant monograph which emphasized his mechanistic theory of life (29), devoted his later years to studies of colloid chemistry (30). Of great biological as well as practical importance during the first decade were Landsteiner's discovery of blood groups (1901) and Carrel's development of methods for vascular anastomosis and transplantation of tissues (1902). The physical and metabolic processes by which glands respond specifically to certain aliments [Pavlov (31)] were thoroughly studied by Bayliss and Starling (33). The
manner in which food is moved through the alimentary tract was greatly clarified by the use of roentgen rays by Cannon and others, and the roles that intrinsic and extrinsic mechanisms play were elucidated by Bayliss and Starling (33). As an outgrowth of his diuresis experiments, a "modern theory" of urinary secretion was formulated by Cushny which added to Ludwig's view the role of colloid osmotic pressure for glomerular filtration and the process of selective absorption by tubules (34).

The invention of the respiration calorimeter by Atwater (1904) offered great promise of future developments which were realized in later years by Benedict, Lusk, Du Bois, and their respective pupils. The headway that had been made by 1906 is summarized in Lusk's monograph (35). He submitted hitherto accepted theories to criticism and altered many of our concepts. Looking back, however, it seems that the experimental results had been pushed somewhat beyond available knowledge of basic organic chemistry. This was true despite the fact that it was an era of great advance in physiological chemistry. For example, Emil Fisher was engaged in studying the building stones of protein and had succeeded in synthesizing a polypeptid in 1903 and a whole protein molecule containing eighteen amino acids in 1907. Lusk's studies on phlorhizinized dogs were basic to interpretations of the process of gluconeogenesis and carbohydrate utilization. However, the significance attached to G:N ratios was to be challenged in years to come. At the same time, Macleod (36) was studying experimental glycosuria from various angles and thus gained the experience necessary to give direction and purpose to metabolic studies that arose immediately after the discovery of insulin (1921). Among the vital concepts enunciated in 1905 to 06 were those of luxus consumption by Chittenden (37), of exogenous and endogenous metabolism by Folin (38), and of the role that factors of safety play in animal economy by Meltzer (39).

The outstanding contribution in the field of endocrinology was probably Starling's concept of hormones. This developed out of observations that the entry of chyme into the duodenum excites pancreatic secretion through dispatch of a chemical messenger called secretin (33, 40). The new information, obtained through injection of extracts from ductless glands, from their surgical removal, and from observation of patients exhibiting glandular disorders, gave increasing evidence of their great importance in the control of body functions, but it was too indefinite to enable one to construct pictures of the modus operandi of these glands. Opinion had crystallized that the thyroid and parathyroid glands have separate functions. The idea that the increased formation of ammonia might be responsible for the tetany which follows parathyroidectomy was short-lived; but the demonstrations of Mac-Callum and Voegtlin that this symptom can be abrogated by injection of calcium solutions proved very valuable in later years.

The advances realized in various fields of the circulation were accomplished through investigations of basic phenomena, through inventions of new apparatus, and through the correlation of physiological studies with clinical applications. Carlson's demonstration of a neurogenic origin and
transmission of impulses in the Limulus heart (41) were soon shown to be inapplicable to the hearts of amphibia and mammals. The discoveries of nodal and conducting muscular tissue in previous eras, supplemented by new studies of impulse initiation and conduction, gave incontrovertible support to the myogenic theory (42). The physiological interpretation of graphic recordings of the pulse enabled Mackenzie to give physiological interpretations to many of the common irregularities (43). Additional experimental studies by Erlanger and Cushny elucidated the phenomena of heart block and atrial fibrillation, and their discoveries soon proved valuable in clinical diagnosis. The foremost step in the decade was the invention in 1903 of the string galvanometer by Einthoven (44) and his prompt application of this new tool to the study of physiological and clinical problems (45), for Einthoven was another rare scientist who was able to apply the combined talents of a mathematician, physicist, physiologist, and physician to the field of physiological investigation. The discerning mind of Thomas Lewis immediately envisaged the great strides that could be made in the field of clinical cardiology through correlation of electrographic phenomena in patients and experimental animals. By the end of the decade Einthoven's work had been enormously extended, both in physiological and clinical fields (46, 47). The design of optically recording manometers by Otto Frank, and of the technique for registering volume curves by Yandell Henderson, supplied a new approach to hemodynamics. However, use of these appliances was largely restricted to the hands of their-designers.

During the first decade of this century the principles for measuring human arterial pressure and for the proper design of instruments for this purpose were practically perfected to the stage in which they exist today. The inherent errors in previous techniques for determining systolic pressure and in the sphygmomanometer of Riva Rocci (1896) and Leonard Hill (1897) were corrected through physical and experimental studies by von Recklinghausen and Erlanger. They also established oscillatory criteria and designed apparatus for the measurement of diastolic pressure. Erlanger and Hooker analyzed the hemodynamics and significance of pulse pressure and suggested that the product of pulse pressure and heart rate is a fair index of cardiac output. Impetus was given to the clinical practice of determining arterial pressures by the publication in 1904 of Janeway's stimulating monograph (48), which also summarized current knowledge. The auscultatory method now generally used was actually described by Korotkov in Russia in 1906 but, owing to latency of translation, remained unknown to us for many years. Incidentally, the validity of this criterion was not established until 1916 through Erlanger's experiments. Hooker and others introduced apparatus for the study of venous pressure in man. Improved forms of flowmeters were invented which allowed more exact measurement of blood flow through various organs. Burton Opitz was particularly productive in this field. The innervation of blood vessels and their control by agents acting directly and reflexly on the vasomotor center were comprehensively studied by many investigators in relation to other functions, among them secretion and shock. [For a partial review, see Bayliss (49).]
A new era of research in nerve physiology was begun. The perspicacity of investigators such as Lapicque and Keith Lucas may be said to have prepared the soil for workers in subsequent years. The effectiveness of electrical stimuli was shown to depend upon parameters of intensity and time. The nature of excitation, the spread of the process over axons, and its transmission over neuromuscular junctions, were in their incipient stages of study. In the field of central nervous system physiology, the publication of Sherrington's classical monograph on the integrative action of the nervous system probably constituted the most significant advance (50). On the whole, further knowledge of the functions of the cerebrum, cerebellum, basal ganglia and spinal conduction pathways awaited the development of new techniques.

The methodology of physiological research was extended more generally also into the solution of practical problems, such as those that relate to exercise, high barometric pressures [as in caisson disease (51)], and other environmental factors on normal individuals. The term "applied physiology" thus came to have two connotations, namely, physiology as applied to problems of everyday life and as applied to problems of disease, also called functional pathology [Wright's *Applied Physiology* (16)].

**THE SECOND DECADE**

My personal experiences during the second decade date from an appointment as instructor under Lusk at Cornell University Medical College in New York City. The incidents surrounding my selection should perhaps be detailed for the benefit of younger physiologists, for they have implications even at the present time. I later learned from Lusk that I had been recommended by Howell because he had been impressed with the quality and manner of my presentations before the American Physiological Society. I mention this so that youngsters may be reminded that it is still common practice to select and promote physiologists on the basis of their public performances at scientific meetings. Perhaps this is also a suitable occasion to express parenthetically my gratitude for the interest that Howell always took in my welfare. It was he who urged my nomination to the American Physiological Society in 1907. Howell took special pains to introduce me to junior physiologists, as the result of which many lasting friendships developed. He was always gracious in making a few kind remarks in discussions of my papers, and, minor though my discoveries still were, he promptly incorporated them in successive editions of his textbook. The exhilaration of seeing one's work quoted in current texts is perhaps puerile but real. Authors of textbooks should keep this in mind as one way of encouraging younger investigators, especially since their small bricks contribute materially toward filling in crevices in the wall of physiological knowledge such as are usually left by epoch-making discoveries of established investigators.

Acceptance of a post under Lusk appeared to offer promise of at least three great opportunities: (a) association with a leading physiologist who had achieved a reputation for fostering research, both in basic sciences and clinical fields, and who, though not himself a medical man, had exerted a profound influence on clinical medicine in New York City; (b) membership in a
department with a light teaching load which thereby could be organized so
that two-thirds of the academic year was available for pursuit of research;
and (c) venture in a new field of training, namely, that of nutrition, in which
Lusk and his group were masters. The last of these had an immediate appeal,
since further progress in circulatory studies appeared temporarily blocked
by the inadequacy of available recording apparatus, whereas use of respira­
tion calorimeters seemed more likely to yield sound information on important
problems of nutrition. It was therefore somewhat disappointing to learn
upon arrival in New York that Lusk had other ideas. Since research on
metabolism was already in progress, he desired to broaden departmental
activities by encouraging research in circulation. Nevertheless, the meta­
bolic atmosphere created by Lusk and Murlin could not fail to diffuse into
the room devoted to circulatory studies. However, it was proper and neces­
sary that I should fit into the scheme of departmental organization and make
plans for continuing my former line of research. Others in similar situations
have probably found that such adaptations are not always accomplished
without some feelings of frustration. However, various unpredictable inci­
dents or accidents usually solve the problem, provided the newcomer is alert
enough to make use of them. I was fortunate in becoming acquainted with H.
B. Williams, who, after a recent visit to Einthoven's laboratory, was redupli­
cating the Leyden instrument at the College of Physicians and Surgeons of
Columbia University. Williams was loaded with information regarding the
theory and construction of string galvanometers and the physical principle
for eliminating extraneous mechanical and electrical vibrations. He was
always willing to talk on these subjects, and I became an equally eager
listener. In fact, except for Einthoven's visit in Cleveland in 1920 and my
reciprocal visit with him in his home and laboratory, my knowledge of elec­
trocardiography stems from my stimulating conferences with Williams.
However, since he was presumably planning to employ the string galvanome­
ter in physiological studies, and since Meek and Oyster in our country
already had a decided start in applying this useful tool to cardiac problems,
I hesitated to press for the large funds required for the acquisition of such
an instrument. It was my privilege, however, a few years later to procure one
of the first three string galvanometers constructed according to specifications
of Williams in the shops of the College of Physicians and Surgeons.

My yearning to serve an apprenticeship under Otto Frank in Munich in
order to gain a more intimate familiarity with new types of apparatus
designed for dynamic studies reached early fruition unexpectedly. Lusk,
having been associated with Frank in Voit's laboratory, found no difficulty
in arranging the opportunity. He also arranged a leave of absence, with
salary, during the last portion of my first year, a generous and unusual pro­
dure at that time, and in addition made available the sum of $500 for the
purchase of necessary new apparatus, presumably a personal donation.

The foregoing incident is related because many earnest younger physi­
ologists must find themselves in a similar quandary as to the procedure by
which training and special techniques may be acquired under masters in the
field. They will generally find that their chiefs will welcome frank discussion of well considered plans and will offer to assist them in their fulfillment, even though this may involve temporary deterioration of departmental efficiency. Fortunately, many agencies now exist for the encouragement of such development. However, it may be expected that those who enjoy such advantages will have a sense of obligation to utilize the training obtained for the advancement of physiology or cognate sciences.

My training in the Physiological Institute at Munich, coupled with privileges extended by Garten in Giessen, opened a new outlook on the construction and proper employment of optically recording instruments. Otto Frank belonged to that group of great physiologists who concentrated more largely on the development of new tools than on their utilization in experimental work. An association with him therefore afforded the opportunity needed to gain a firsthand acquaintance with his newly developed apparatus and to understand the principles of its construction. The latter proved highly important, for repeated modifications in the design of Frank's instruments were required before they were applicable to the experimental and clinical problems I had in mind. The first application of optically recording manometers was made to studies of the dynamics of valvular lesions and hemorrhage. However, a short period of such investigation made it evident that an analysis of results required more detailed knowledge of normal mechanisms that we had at that time. Therefore, the following few years were devoted largely to acquiring this needed information. Returning to the study of so-called practical problems, such a need for more basic research has arisen again and again. Thus, whereas it was my avowed aim to contribute chiefly to the solution of clinical problems, most of my investigations have reverted to basic fields. While our lack of fundamental knowledge is disconcerting when it crops up during investigations of practical problems—either in the laboratory or clinic—it is comforting for physiologists to know that not all basic research is at an end.

Having gained some experience in hemodynamic studies, both in animals and hospital patients, I decided in 1915 to incorporate the current knowledge of the circulation in health and disease in a monograph (52). In this connection the observation may be made that it is a duty as well as a privilege for experienced investigators to present occasionally an analysis of the subject in which they are proficient in the form of monographs and reviews in order that others may become acquainted more easily with recent advances in the subject.

Younger investigators derive great benefit from frequent contacts with active workers in their communities. In general, such opportunities for repeated exchange of ideas increase with the number of research centers in a circumscribed geographical area. New York City during 1911 to 18 afforded splendid opportunities for development of intimate acquaintance with one's contemporaries and their work. Also, the "Meltzer Verein" (the Society for Experimental Biology and Medicine) which then held its meetings in different laboratories of the city, served as a good mixer, while the Harvey Society...
brought distinguished guests as lecturers. In this connection, the observation may not be wholly gratuitous that the value of a lecture depends less on the summary of current knowledge than on the stimulation of the listener to delve somewhat deeper into the subject in the quiet of the library. Truly, a good library is also an invaluable asset for the development of an investigator.

Despite the many advantages of an academic career, the disparity between salaries and cost of living and the small chance of becoming an incumbent of one of the few available chairs impel many a younger scientist to accept a more remunerative nonacademic post. I did not escape consideration of such a deflection to commercial fields or medical practice. Lusk's advice to me, which I have passed on to succeeding generations, was: "Hold off until forty. Then, if not in a favorable academic position with tenure for life, consider such a change carefully." I commend this rule to perturbed younger physiologists.

With our entry into World War I the administrative and teaching functions of a department again devolved upon me, and the time available for research was devoted to experimental studies on shock. Unfortunately, most of my hemodynamic studies tended to confuse rather than clarify the issues. However, the privilege of attending many group conferences of a national committee on shock under the chairmanship of Howell proved of great personal benefit. Among other benefits, it caused previous acquaintances with such scientists as Hooker, Macleod, Yandell Henderson, and Torald Sollmann to grow into lasting friendships. In particular, Sollmann's sagacity, discriminating judgment, and happy optimism proved invaluable in succeeding years. Later it was my privilege to join Major Peabody in the U.S. Army Hospital at Lakewood, N. J., in efforts to elucidate the nature of functional disturbances of the heart in soldiers. Unfortunately, no great headway was made in the real solution of the problem, either by our group at Lakewood or by that of Thomas Lewis in the Military Heart Hospital at Hampstead, England (53). However, the brief association with Peabody gave me an insight into the trend that modern medicine was likely to assume and the part that the physiological study of patients was destined to play. The manifold influences that Peabody exerted on the future trends of scientific medicine were obvious to us during the Lakewood association. He had, for example, the ability to surround himself with a remarkable group of interns and assistants, such as Clough, Stroud, Sturgis, and Wearn, each of whom has attained pre-eminence in the field of medicine. When it appeared clear in the fall of 1918 that the war would soon terminate, I felt no compunction in accepting a professorship at Western Reserve University. The second decade of the present century was now nearing an end.

Among the advances in physiology that impressed me most during this decade, I should perhaps mention first the great strides in explaining physiological phenomena in biochemical and biophysical terms. The publication of Bayliss' book on general physiology (10) and that of Burns on biophysics (54) excited the greatest interest. These authors defined the scope of subjects
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that can be included in these respective areas. The monograph of Lucas (55) revealed the new thinking with regard to the nature and passage of the nerve impulse. Hasselbalch, Michaelis, and Mansfield Clark contributed in numerous ways to the application of pH measurements in biological systems. L. J. Henderson formulated the chemical reactions by which pH in buffered solutions and acid excretion of the body maintains its constancy (56). His conceptions were extended by Van Slyke's procedure of determining the degree of acidosis and of available alkali reserve in terms of carbon dioxide combining power.

The concept of the glomerular filtration of dilute urine was placed on a firm foundation by a variety of experimental procedures [Cushny (34)]. The demonstration that glomerular capillary pressure is regulated by differential effects of stimuli on afferent and efferent vessels and that an intermittency of glomerular flow occurs in the frog's kidney removed some of the weighty objections that had been raised against the filtration hypothesis (57). In 1912, Ambard and Weil suggested an equation which related the rate of urea excretion to blood urea in a dynamic sense. After additional studies of McLean, Addis, and Van Slyke, the volume of blood cleared of urea by one minute's excretion came to be expressed as urea clearance (1921). The far-reaching importance of this methodology in the assessment of renal function could not be appreciated until the later decades of this century. Early in this decade it was my privilege to observe a demonstration by Abel and his colleagues of a vividiffusion apparatus which, though primarily designed to study the absorption of amino acids, unquestionably suggested the construction and use of artificial kidneys in the present era. Meanwhile, Sabin's study of the growth of the lymphatic system (58), establishing the noncontinuity of lymphatic and tissue spaces, was destined to influence basic concepts of lymph formation and edema.

Renewed studies were made of the problem as to how chemical energy is converted to muscular work during contraction, but the chemo- and thermodynamic studies of muscle and nerve came to fruition only in succeeding decades.

The studies of Howell (59) gave us a clearer insight into the process of blood coagulation, the chemical factors concerned, and their reactions, but he could not realize at the time that the process would turn out to be far more complicated than his theory of coagulation implied. During this period the natural destruction of red cells by fragmentation rather than by hemolysis was demonstrated by Rous, but the life span of red corpuscles appeared to vary with the technique employed.

Continued improvements in gasometric apparatus and experimental procedures seemed to have proved conclusively [see Haldane (60), Barcroft (61), Krogh (62)] that the respiratory center is dominantly controlled through humoral mechanisms. The difficulties in such interpretations, which subsequently led to revision in our conceptions that other factors, including nervous regulation, are also important, occurred chiefly in later decades. For example, Gesell first proposed the hypothesis that the respiratory center
is regulated by intracellular acidity in December, 1922. The suggestion of Bohr (1909), also supported by Haldane, that under certain conditions the pulmonary epithelium has a secretory power in transferring oxygen, was put to test by successive scientific expeditions to Pike's Peak (1913) and to Cerro de Pasco in Peru (1914). The problem appeared to be finally settled by Barcroft, who lived for six days in a low pressure chamber (1920). However, the problem continued to excite interest up to the present war, when it was again investigated by making use of significant improvements in technique.

In summary, it appeared that physiologists were ready to accept as the orthodox creed that physiology is only a special application of ordinary physics and chemistry (10, 21, 29, 63) and were inclined to regard any deviation from this creed as scientific heresy. Haldane, however, denounced such a conception and urged physiologists to view the organism as a whole and not to be carried away by mechanistic concepts derived from the studies of isolated tissues. He called the attempts to analyze living organisms as physical and chemical mechanisms a colossal failure and urged that the new physiology be regarded as biological physiology—not biophysics or biochemistry (64). My own considered reactions have always been that something may be said in favor of such a view, but not a great deal.

Progress in the study of metabolism proceeded in so many directions that any brief summary is necessarily inadequate. Many of the mysteries of the intermediary metabolism of fats, carbohydrates, and proteins were unraveled through development of new chemical procedures. Only a few high points that impressed me can be mentioned. Knoop's concept of beta oxidation of fatty acids (65) remained unchallenged. The fate of absorbed amino acids was elucidated (66). The grouping of amino acids as dispensable and indispensable for growth was realized in part. Gluconeogenesis and combustion of carbohydrates by tissues was intensively studied, particularly in relation to clinical, phlorhizin, and pancreatic diabetes. The mechanism of ketosis and the ketolytic products which prevented its occurrence under normal conditions were analyzed (67, 68). Investigators most intimately concerned with the study of diabetes had the feeling that the nature of the pancreatic hormone was on the verge of discovery, which actually eventuated in 1922. The mechanism of oxidation received a great deal of attention; new enzymes were discovered and new theories set up. However, the suggestion made by Ostwald in 1898, that oxidation can be expressed basically only in terms of electrical charges, was largely bypassed except by a few brave souls.

The study of respiratory metabolism in disease, begun by Benedict and Joselyn in 1910, received a great impetus through construction of a respiration calorimeter in New York and its utilization by DuBois and his associates. These studies yielded much information regarding human diabetes mellitus, typhoid fever, malaria, anemia, and cardiorenal diseases, and supplied a rational foundation for providing proper nutrition for patients with different disorders (69).

Of far-reaching importance in the future outlook upon nutrition was the
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Growing recognition that foods contain factors accessory to energy-yielding and tissue-building components and, particularly, Funk's designation of the missing accessory factor in polished rice as a "vitamin E" (1911). Exciting discoveries occurred in rapid succession. During 1913 to 16, McCollum and his associates discovered a growth-promoting factor in butterfat and eggs which they called fat-soluble A, distinct from the water-soluble component called water-soluble B in a diet producing beri-beri (70). During 1914 to 18, Hess (71) demonstrated the presence of a water-soluble vitamin C in fruits and tomatoes, deficiency of which led to scurvy. In 1919, Mellanby discovered that cod liver oil contains a factor, vitamin D, which caused marked improvement in experimental rickets. Only a few years later (1922), Evans and his associates located another vitamin (E) in wheat germ and lettuce leaves which was concerned with reproductive power and sterility. Thus, by 1922 vitamins A, B, C, D, and E had all been discovered, and a suspicion existed that B was composed of two elements, an antineuritic and a pellagra preventative component (Goldberger). The practical and clinical value of these discoveries quickly became apparent.

Outstanding advancements in the field of circulation were realized through the more general availability of string galvanometers and their employment by competent investigators with imaginative minds; the design of new forms of optical myographs, pressure manometers, heart sound recorders, and their employment both in laboratories and clinics; and the development of clever procedures by means of which the operation of the heart beat could be studied. The famed heart-lung preparation, which Starling once demonstrated to me during a visit to his laboratory, was among the latter.

An idea as to the breadth of the advancing front can be gained from a list of the circulatory problems attacked and at least partially solved. Knowledge was extended with regard to (a) the spread of the excitatory process over the atria and ventricles, (b) the nature of cardiac irregularities, (c) the relation of electric and dynamic cardiac events, (d) the fractionate character of atrial contractions and their dynamic importance, (e) the details of sequential phases of the cardiac cycle, (f) the forces concerned in closure of cardiac valves, (g) the changes in sounds in their transmission from the heart to the chest wall, (h) the factors which determine the intensity of heart sounds, (i) the precise timing of murmurs in valvular heart disease, and (j) the control of the pulmonary circulation (72). Advances in the dynamics of the heart beat included (a) the conception and determination of the effective atrial pressures; (b) the reactions of the ventricles to changes in initial tension, initial length, aortic resistance, and heart rate, as manifested by alterations in stroke volume and modes of ventricular filling and ejection; (c) the interpretation of cardiac tonus and its role in cardiodynamics; and (d) the formulation of Starling's law of the heart and the author's concept of the autoregulation of cardiac compensation and decompensation (73, 74, 75). Studies on cardiac metabolism, coronary flow, and capillary circulation remained in incipient stages of the tremendous progress yet to be achieved in the next decade (76, 77, 78).
The second decade also saw the birth of the new specialty of clinical cardiology, which also included studies of peripheral blood flow in vascular and cardiac disorders (Hewlett, Stewart). Clinical problems such as dynamic effects of cardiac irregularities and valvular insufficiency were returned to the laboratory for more basic study. The circulatory changes produced by anoxia and shock were studied intensively both in animals and man. At the close of the decade it was the consensus that the decline of arterial pressure in shock is caused by reduction in circulating volume, occasioned either through loss of fluid or increase in vascular capacity [Bayliss (79)]. It was believed that capillaries dilate and become more permeable through release of histamine-like substances (80) and that these processes lead to progressive reduction in venous return and cardiac output (81, 82).

The smog that had enveloped the ductless glands began to lift a little. The rate of progress can be judged by comparing the monographs of Biedl (83) and of Sharpey-Schafer (84) with surveys of the subject in the Harvey Lectures of 1923 to 24 by Biedl, Marine, Abel, and H. M. Evans. In 1916, Sharpey-Schafer (84) proposed that internal secretions be designated as auto­coids, which include hormones that excite and chalones that inhibit. The headway during this decade may be indicated by a few sketchy notations concerning some representative endocrine organs: it had been established that the adrenal cortex and medulla have separate functions, but, aside from an apparent relation to sex organs, the function of the cortex remained obscure. Macleod (12) in 1918, for example, made the frank statement: "Some facts indicate that it has other functions." It was well known that the medulla elaborates a principle, epinephrine, the secretion of which is under the control of nerves. Researches of the period were largely concerned with the biological assay of epinephrine in the blood and led to the controversy between Cannon and Stewart as to whether the medulla had an emergency function or none at all (85, 86). No conclusive evidence existed at the close of World War I that the adrenal medulla is implicated in shock.

The outstanding contributions to the physiology of the thyroid consisted in the isolation and physiological study of thyroxin by Kendall (87), and in the demonstration by Marine and his associates (88) that iodine is important in determining thyroid activity and in the prevention of colloid goiter. Rival theories developed, holding that the symptoms following parathyroidectomy are due to (a) guanidine intoxication (Noel Paton) or (b) to calcium deficiency (MacCallum and Voegtlin). The problem was soon to be settled by Collip's discovery of a parathyroid hormone (1926).

Considerable clarification regarding the functions of separate parts of the pituitary resulted from the clinical and experimental studies of Houssay (89) and Cushing (90) and their pupils. It appeared to be the consensus that the anterior pituitary principles controlled the growth of bones and musculature and the development of the sexual organs, while the principles of the posterior lobe are concerned with regulation of urinary secretion and the metabolism of carbohydrate and fat. Cushing visualized the pituitary gland as the conductor of the endocrine orchestra, a concept of master function which is retained to the present day.
The techniques of tissue culture and experimental cytology were developed and an incipient attempt made in the biostatistical analysis of experimental results (Pearl). During this period, Cannon (91) philosophized on the meaning of his many experiments in a monograph dealing with the bodily effects of fear, hunger, pain, and rage. Carlson (92) restudied the phenomenon of hunger in its broad biological as well as practical aspects.

A few general remarks concerning physiological advances during World War I shall conclude this narrative. When a nation enters into a modern war it invariably finds itself unprepared to meet new emergencies created by unforeseen developments and construction of deadlier weapons. This applies not only to military equipment and tactics but also to professional skills and scientific knowledge. Consequently, new knowledge must be acquired rapidly and applied to military situations. The field of research into which physiology fitted during World War I covered, among others, problems of food supply for soldiers, the nature and treatment of hemorrhage and shock, the effects of and treatment of poisoning with lethal war gases, the results of high explosives upon the ear and central nervous system, and the problems associated with new development of aerial warfare. Altitude physiology became an acute subject because a military advantage was gained by the aviator who could climb above his adversary and choose the moment of attack. While aerial combats took place at comparatively low altitudes at the beginning of World War II, planes capable of ascending as high as 15,000 to 18,000 feet were developed before its close. Our preparedness in the field of altitude physiology rested largely on the monumental monograph published by Paul Bert in 1878 (93), which, incidentally, was regarded so highly as an old testament that a translation was ordered during the last war by Hitchcock (94). A new testament of facts was also available as a result of additional studies made by various expeditions to mountain peaks. The knowledge of nitrogen embolism derived from studies of sudden decompression of divers was as yet of no great importance, since fighting planes could scarcely attain an altitude of 20,000 feet. The chief problem for physiological investigators, therefore, consisted in testing candidates for the air service with regard to their response to low barometric pressures in decompression chambers and to low oxygen mixtures breathed from spirometers. The practical problem that confronted the Mineola Research Laboratory during this emergency was to determine the effects of rapidly decreasing oxygen tension on the heart rate, arterial pressure, heart sounds, muscular coordination, and psychic reactions of persons rated as good, average, and poor, and to systematize and apply these standards on a large scale in flying fields in France. The work accomplished by this laboratory during its brief existence (95) was not only of immediate military value but also of immense significance in expanding our physiological knowledge and, most important, in stimulating interest in aviation physiology as a specialty. This led eventually to the creation of a number of aviation research laboratories in various institutions and in special governmental laboratories under the supervision of the Civil Aeronautical Authority (Medical Science Station, C.A.A., Kansas City, Missouri, 1938); the Army (Wright Field, Dayton, Ohio,
1934; School of Aviation Medicine, Dallas, Texas, 1939); and the Navy (School of Aviation Medicine, Pensacola, Florida, 1939).

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