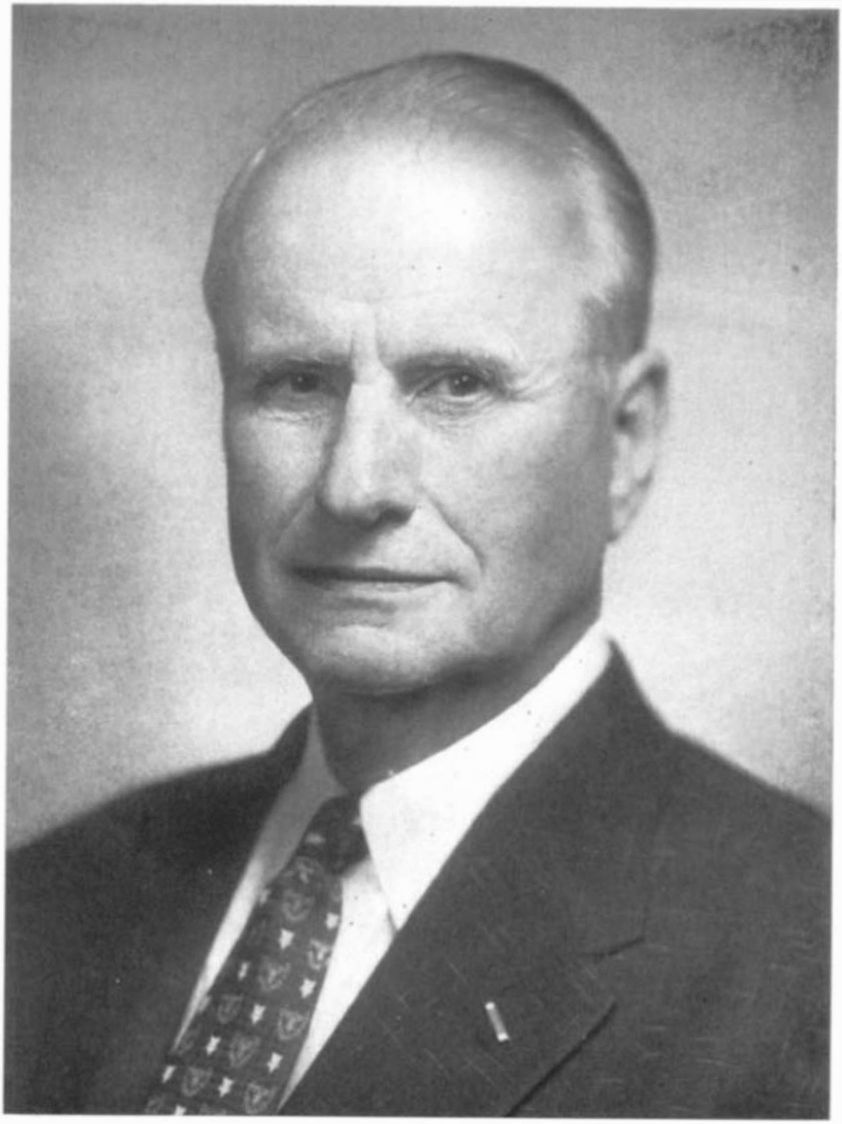

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PREFATORY CHAPTER

PHYSIOLOGY AND MEDICINE: A TRANSITION PERIOD

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It has been my privilege to live and work through a transition period of American medical science. My participation in and observation of the revolutionary changes that have taken place in medicine and physiology during the past fifty years (1910 to 1960) is my justification for accepting the invitation of the Editors to write a highly personal account of this period.

In 1910—the year in which Abraham Flexner's report on medical education (1) was published—I received the M.D. degree from Rush Medical College of the University of Chicago, and I have been continuously engaged in full-time physiology and medicine since then, including service in the United States Army Medical Corps during two wars. The competition for admission to the scientific societies in my first decade was not as great as it is today; this accounts for my election to the American Physiological Society in 1914, to the American Society of Biological Chemists, the American Society for the Advancement of Clinical Investigation (now the American Society for Clinical Investigation) and to the American Society for Pharmacology and Experimental Therapeutics in 1916, and to the Association of American Physicians in 1919.

My first professorship—in pharmacology and materia medica—was in the University of Oregon Medical School, at Portland, Oregon, in 1911. Mr. Flexner had written that this school had neither resources nor ideals, and that there was no justification for its existence. My appointment began on December 1, 1911, with quarters in the "frame building, wretchedly kept", as described by him. Having begun my academic life in one of the situations that the Flexner report was destined to correct, I have advanced, in both physiology and medicine, through some of the best that American medicine has produced during my lifetime.

The most important achievement of this transition period in physiology and medicine has been the development, on an equal but independent basis, of two great sciences, or groups of sciences. The one, concerned with disease and with diseased states, we call medicine. The other, concerned with the normal or healthy state, we call physiology. It is not within the scope of this chapter to relate the events or to name the individuals, both in America and abroad, leading to the accomplishments of the past fifty years. That the time was ripe for an advance in the sciences concerned with medicine, and in medicine itself, seems clear from the fact that several events, destined to influence this advance, occurred almost simultaneously. The American Society for the Advancement of Clinical Investigation held its first annual meeting in 1909; and S. J. Meltzer, in his presidential address, set forth the need for "a differentiation of clinical medicine into a science and a practice" (2). In 1910, the year of the Flexner report, the Hospital of the Rockefeller Institute for Medical Research was opened in New York, with Dr. Rufus Cole as Director. In the same year the University of Pennsylvania, in Philadelphia, established a chair of research medicine. The Council on Medical Education of the American Medical Association, appointed in 1904, played a large part, not generally recognized, in the survey leading to the Flexner report and an even greater part in the subsequent efforts to improve the conditions recorded in the report.

In 1913 The Johns Hopkins University School of Medicine procured the funds which enabled the maintenance of a full-time group of teachers and investigators in medicine, surgery, and pediatrics, and by 1925 Mr. Flexner was able to account for more than thirty full-time clinical chairs, many with numerous full-time assistants, in the United States, Canada, and England (3). In the same volume he stated that:

> There are . . . a few clinics in the United States which, despite the obstacles and defects from which in greater or less degree all schools suffer, have undertaken to train medical students in the spirit and method of scientific medicine. Towards this end they possess . . . more complete laboratory facilities—chemical, physical, and biological—than are found anywhere else in the world devoted to medical education as such. . . . The student is therefore, in so far as these clinics are concerned, getting his education in close contact with, and to some extent in real participation in, the scientific study and treatment of disease from one or another fundamental point of view.

In the meantime, in 1920, Rufus Cole had provided a blueprint for a University Department of Medicine, in keeping with the newer conceptions of medicine as a science, for which he was so largely responsible (4). He wrote: "It is of importance that medicine should now be generally recognized as an independent science, just as physiology and anatomy are independent sciences." He rejected the designation of medicine as an applied science and emphasized the importance of investigating disease and diseased states as natural phenomena, worthy of study for their own sakes, and without necessary concern with the immediate practical applications that had previously dominated most inquiries into the subject-matter of disease.

In advancing this viewpoint Dr. Cole wrote an eloquent paragraph that has been frequently cited and must here be quoted in full. He said:

> Are men available for such a department, as teachers and students, men who are interested in the study of disease and who desire to increase the knowledge concerning disease without any other material reward than the rewards of the student and scholar? Or has scholarship gone out of fashion? Or is this such an uninteresting subject that no men can be found to undertake its study? As long as men will study the stars with scientific methods, as long as men will study the stones with scientific methods, men will be found to study disease. The men are ready and waiting, the opportunity only is needed.

Dr. Cole followed this paragraph with a statement concerning the need of laboratories for the program he envisaged, and said:

> The student of medicine must also have *his* observatory, the hospital, and in this he should also have laboratories—*his* laboratories—and not be a guest or intruder in laboratories belonging to other scientific workers—chemists, physiologists or others. . . . For the development and teaching of medicine, laboratories are as essential as they are for the study of physiology . . . they must be so arranged and organized that the work in the laboratories and in the wards can go on simultaneously and harmoniously in both.

There is thus much evidence that within the first ten to fifteen years that followed the Flexner report a new science was already in the making, the science of medicine, which has become something more than the application of physics, chemistry, biochemistry, and physiology to the problems of disease. I believe that the essentials for university departments of medicine, embodying the principles laid down by Dr. Cole both as to personnel and to physical facilities, have been accepted in every university and school of medicine in the United States; in fact they have been accepted and put in practice in a number of hospitals without teaching connections. There has inevitably been a lag in realization of Dr. Cole's objectives, and his ideal plan, as set forth forty years ago, has been met only to varying degrees in various institutions. As a whole, however, the situation in medicine in the United States today corresponds to a remarkable degree with Dr. Cole's ideas.

Nor has this been accomplished to the detriment of physiology and of the other nonclinical sciences. The physiological sciences, liberated from the need to cater to medicine, have grown, both in quantity and in quality, in a manner parallel to the growth of medicine. The situation in 1928, at a time somewhat later than that in which Dr. Cole was writing, was described in an admirable manner by Professor C. A. Lovatt Evans, in a presidential address delivered before the Section on Physiology of the British Society for the Advancement of Science (5). In a comment on this address, Dr. Alfred E. Cohn (6) found that:

> although physiology has made itself independent, Professor Evans still harbors fears. He fears to cut the guiding strings of the alma mater [medicine], lest physiology lack nourishment. And like many, especially modern, children, he fears lest the ancient mother be too feeble intellectually and too powerless, having reared and weaned her children, to be able to continue to order and to develop her own house. But the situation is just this: having learned as it were and indicated to her many offspring how they might best set up houses of their own, medicine is at length free to cultivate her own garden.

That Professor Evans' fears were groundless is made evident by the contents of the *Annual Review of Physiology*, from Volume I, 1939, and of the *Annual Review of Biochemistry*, from Volume I, 1932. The growth and development of medicine and of physiology have been complementary, each having been nourished in part by the other, and both are enjoying interest and support seen only as an ideal toward which to strive when Dr. Cole published his paper in 1920. It has been my good fortune to be associated with both physiology and medicine, and with some of the leaders in both disciplines during this period of evolution and thus to have witnessed some of the accomplishments from a favorable position. What I have to say about my own activities may be of interest for this reason.

I came into intimate contact, at an early age, with some of the best representatives of the medical sciences, in the departments representing the biological sciences in the University of Chicago. Eugene F. DuBois has written that his "medical school course in physiology in 1903 consisted of dry lectures and distant demonstrations of a few animal experiments. Biochemistry and pharmacology, which even then were separate courses, added but little light" (7). My own experience was the exact opposite of this, yet the careers of Eugene DuBois and myself were in some respects parallel.

Among my teachers in the preclinical years was, first and foremost, Anton J. Carlson (physiology). Others, with most of whom I had close contact, were F. R. Lillie (zoology), C. J. Herrick (neurology), B. C. H. Harvey (histology), R. R. Bensley (anatomy), G. N. Stewart (physiology), A. P. Mathews (physiological chemistry), H. G. Wells (pathology), E. O. Jordan (bacteriology), and Waldemar Koch (pharmacology). This was the period during which the biological sciences at the University of Chicago reached heights rarely equalled there or elsewhere, before or since, and every encounter with this galaxy of stars was to me a stimulating experience. The University of Chicago had more than its share of talent in the biological sciences; partly because of President Harper's raid on Clark University, with his provision of more favorable conditions, both for living and for working, partly because of a generous endowment from Helen Culver in 1895 "to be devoted to the increase and spread of knowledge within the field of the Biological Sciences", and partly because of the opportunity given to these sciences to develop in true university departments, without the domination of the immediate needs of medical education. It is safe to say that no other medical school in the United States, in that era, had the advantages accruing to medicine from strength in the biological sciences like that of the University of Chicago.

It was in this setting that I encountered the man who was to have the most profound influence upon my subsequent career. From my first contact with A. J. Carlson he was a source of stimulation and guidance to me, and the relationship continued until his death in 1956. As a student, I accompanied him frequently to the stockyards, where he was studying salivary secretion and lymph formation in horses marked for slaughter, and this was my introduction to research. In January, 1908, before I had reached the age of twenty, I made my first appearance in print as a co-author with Carlson, and six months later a second paper appeared, with myself as sole author. Dr.

Carlson's generosity in publishing this second paper with my name alone, because it was based on an idea I had proposed to him, not only made him my friend for life; it confirmed me in my desire to be a physiologist. He had spent as much time on the problem as I had, and had in fact contributed most to the planning and conduct of the experiments; his generous action was characteristic of the man.

I have said that I took up a position at the University of Oregon in 1911. I remained in this position, with some important interludes, until 1914. On arrival in Portland, following termination of an internship in the Cook County Hospital, I found that a laboratory had to be established and equipped *de novo* and that a room on the third floor of the frame building, under the eaves and with dormer windows, had been assigned for this purpose. The State of Oregon had appropriated a total of $20,000 to the Medical School for the academic year and this, together with student fees, constituted the total income for the school. Funds were scarce, and I bought kitchen tables for laboratory benches, in addition to physiological apparatus from the Harvard Apparatus Company and conventional glassware. By the beginning of the second semester I had a workable one-room laboratory for instruction in pharmacology, and I gave my first course in the spring of 1912, supplementing the laboratory work with lectures.

In the summer of 1912 I returned to the University of Chicago, where I gave the course in pharmacology; Waldemar Koch, with whom I had served as a student assistant, had died after I left for Oregon. In January, 1913, I left for Europe, to spend the winter with Professor Otto Loewi in his laboratory at the University of Graz in Austria, and I remained with him until after we both attended the International Physiological Congress in Groningen in the summer of the same year. Although only one short publication resulted from the stay with Loewi, the association with him and the opportunity to observe medical education and research in Graz and in other European centers had a profound influence on the shaping of my subsequent career.

I remained in Portland for the full academic year of 1913–14. Under the stimulus of my stay with Professor Loewi and aided by an association with a young internist, Dr. Laurence Selling, I began to carry on research in the same one-room laboratory in which I gave instruction to the medical students. During this period I published a paper on the blood sugar in diabetes mellitus, using the Bertrand method, which required reduction of copper, followed by its filtration and weighing. Homer W. Smith has referred to this paper as recording the first blood sugar determinations in this country (8). With Selling I published a paper on the excretion of urea in the urine as related to its concentration in the blood. This work made use of the newly-published method of Folin, and initiated the application of the Ambard coefficient which eventually led to the studies of Van Slyke and his collaborators and to the methods for estimation of urea clearance still in use.

By the summer of 1914 I had made plans to spend the next two years in Breslau in internal medicine, with Otto Minkowski. I resigned from the

University of Oregon and returned to Chicago to await a sailing from New York booked for August 14, 1914. Before this date World War I was under way, and my plans underwent a radical change. I called on Drs. Rufus Cole and Donald D. Van Slyke at the Hospital of the Rockefeller Institute for Medical Research in New York, and secured an appointment to an assistant residency at the hospital, to replace an incumbent who had returned to Germany at the outbreak of the war.

Then followed two fruitful years. In addition to the association with Drs. Cole and Van Slyke, I very quickly formed a tie with Dr. Alfred E. Cohn, who was studying heart disease. It was by a combination of work with his patients and in the laboratories of Dr. Van Slyke that I was enabled to carry on studies on the excretion of urea and chlorides in the urine. These studies resulted directly in a number of publications and led eventually to the further extension of the work by Van Slyke and his associates. During the same period I was serving as an assistant resident on Dr. Cohn's service and became familiar with contemporary work on heart disease, and with electrocardiography, in which Dr. Cohn was one of the pioneers. Alfred Cohn was one of the foremost proponents of the science of medicine and of the university department of medicine, and I remained in close association with him and under his influence until his death in 1957.

In retrospect it seems that I left the Rockefeller Hospital and the opportunities afforded to me there much too early. But because I did so I was able to participate in the implementation of some of the ideas I had been exposed to, and was accumulating, by taking part in the developments in Peking and Chicago. In 1916 I was asked to go to China to aid in the establishment of the Peking Union Medical College, and the years 1916–23, which included active duty in the Army in World War I, were spent in a variety of activities, since I did not go to Peking to remain there for any length of time until the winter of 1920–21. Most important for my scientific development was the opportunity to spend the winter of 1919–20 with L. J. Henderson at Harvard University in the company of H. A. Murray, Jr. The story of this winter and of the subsequent developments has been told in detail by Henderson in his book on *Blood* (9). A whole new field was opened by Henderson's deductions concerning the effect of oxygen upon the dissociation of hemoglobin as an acid, and I participated in the very first steps in the proof of Henderson's deductions and in the work that followed.

L. J. Henderson was one of the world's truly great figures in physiology, and in my opinion has never been given the recognition he deserved. His great contributions were to an understanding of the acid-base balance of the blood and of the physiological significance of the variable acidity of hemoglobin. In both instances his contributions were mainly those of his mind rather than of the laboratory, but in both he was responsible for opening vast areas for further investigation. The privilege of working with him and of observing him in action was responsible for giving me guidance and direction in my further activities.

Since the new buildings of the Peking Union Medical College were approaching completion, it was necessary for me to return to China early in 1921. Before leaving the United States it was agreed with Henderson, as related in his book, to transfer the work on hemoglobin to Van Slyke's laboratory at the Rockefeller Hospital. There began a collaboration which included, among others, Austin, Cullen, Hastings, Peters, and Van Slyke. My own participation at the Rockefeller Hospital ended with 1920, but in the winter of 1922–23 Van Slyke came to Peking as a Visiting Professor, and as the result of work done there the definitive paper of Van Slyke, Wu, and McLean was published. The privilege of working with Van Slyke in 1914–15, in 1920, in 1922–23, and still later in 1924–25 was in many respects responsible for the direction my work took later. There is no need for me to dwell upon his own contributions to clinical chemistry and to medicine; I do wish to give him credit for aiding in the development of whatever talents I may have possessed. The influence upon me of Van Slyke and of Henderson did much to compensate for the time lost in the less rewarding pursuits in connection with the planning and organization for Peking.

Peking, however, was important in another connection since it gave me an opportunity to plan buildings to incorporate some of my ideas. From the beginning these buildings were planned to provide laboratories, both for research and for diagnosis, treatment, and teaching, as an integral part of the facilities for each of the clinical branches of medicine. Operation of these laboratories by the clinical departments demonstrated the soundness of the plan; the fault lay in the failure to provide enough such facilities for these departments. In any event it was not necessary for the clinician to borrow space and laboratory facilities from the physiologist in order to carry on his own investigations. The principles laid down by Rufus Cole in 1920, to which I had of course been exposed since 1914, were thus given full expression in the laboratories and clinics formally opened in 1921. The importance that I attributed to this at the time is reflected in the following sentence in a letter which I wrote to Abraham Flexner on February 20, 1924: "In the plans for Peking I insisted on, and got, unity in the main clinical departments, which did not exist in other places at the time."

Leaving Peking in 1923, I assumed a professorship of medicine at the University of Chicago in November of that year, with some responsibility for establishment of the new clinical departments of the University, which had been delayed because of World War I. On my arrival in Chicago I found that shortly after 1920 architectural plans had been completed for a hospital on a site across the Midway Plaisance from the main quadrangles of the University. These plans included wards and an outpatient department for the use of the clinical departments, and a laboratory building assigned wholly to the Department of Pathology. They thus conformed to the scheme of operations that had been common in the United States up to that time. The clinicians were expected to take care of patients and to teach clinical medicine at the bedside; the laboratories were the responsibility of the non-clinical departments; if anyone in a clinical department had the ability and the desire to engage in research he could borrow laboratory space from the Department of Pathology. The other medical sciences were located at a considerable distance from the site on which the hospital was to be built.

Here my experience in Peking stood me in good stead. With the support of the University Senate Committee, which had made recommendations concerning the goals of the University of Chicago in medicine, I was instrumental in having these plans discarded. This made possible both a more favorable site for the new hospitals and clinics, and a complete revision of the plans. The first clinical units, embracing medicine and surgery and some of the specialties, as well as pathology, were built on a new plan and were opened in October, 1927. The new plan was based on the principle that each department would have its own house, providing for hospital patients, outpatients, and laboratories, and in each instance the space provided for laboratories was approximately equal to that for patients. The idea of a separate house for a department or clinic was of course not new; clinics had been built in Europe on this plan for many years. For America it was new to provide ample laboratory facilities as an integral part of the space allotted to each of the clinical departments; this plan has been continued and extended for each of the clinical units built later at the University of Chicago. The plan of the separate European *Klinik* was modified, in the Chicago plan, by arrangements for common facilities for administration and for the machinery of admission of patients.

It turned out that the provision of laboratory facilities for each clinical department was not enough to insure that the department would be master in its own house. There was pressure from the bacteriologists, who wished to move into the new laboratories of the Department of Medicine and to assume responsibility there both for the study of infectious diseases and for operation of the diagnostic laboratories for clinical bacteriology and serology. Similarly, there was pressure from the physiological chemists, who wished to assume the same responsibility for the study of metabolic disease and for the operation of the laboratories of clinical chemistry. In my opinion, resolution of these conflicts in favor of the plan that obtains today, both at Chicago and in many other institutions, marked a critical point in defining the role of the "full-time" clinician, and I believe also that the non-clinical departments have profited to an equal extent by being relieved of the responsibility of providing service functions for the hospital. Above I have attributed the strength of the biological sciences at the University of Chicago in part to the fact that they were not required to be the handmaidens of medicine; to have yielded on this point would have meant a regression to the practices widely current in American medicine during the era before 1910. Since the biological sciences were already established as university departments, and since the addition of the clinical departments was conceived of as an extension of this plan, these departments were organized in the Ogden Graduate School of Science, part of which later became the Division of the Biological Sciences. Included in this division is the School of Medicine, the faculty of which controls the M.D. degree, but the School of Medicine is not an administrative unit. This form of organization, which recognizes the departments representing the various branches of medicine and surgery as true university departments, is unique in American medicine and is an expression of the place of medicine as a biological science.

The new clinical facilities and the Departments of Medicine and of Surgery were launched, with appropriate dedication ceremonies, on October 21, 1927. Dr. Cole spoke at these exercises (10) and closed by saying: "The University of Chicago has consciously inaugurated a new idea; it has established a true university department of medicine; it has erected an observatory and laboratory for the study of disease." Dr. Alfred Cohn also spoke, and emphasized that the phenomena of the diseased state form the subject-matter of a science, to be pursued for its own sake (11). He said:

> . . . there is a general impression that the study of disease leads for the most part to a career only in the practice of medicine. That the phenomena of life exhibited by diseased cells may be investigated apart from this motive, that they can be studied as can any other biological system, is not a familiar belief. And yet there is no doubt that they lend themselves to this purpose. Disease is also a state of nature. The study of diseased systems may, indeed, yield information of first-rate importance concerning the behavior of living organisms. Both are natural and might for the purpose of biological generalization be equal. This is an idea which may very well become the basis of a conscious direction in the study of medicine of which until now no advantage or relatively little has been taken. . . . If it becomes recognized that the study of diseases offers these opportunities, medicine at once will be seen to take on new aspects. Men entering the study with widely different purposes will aid in the pursuit of its aim. It becomes unnecessary any longer to center interest in diseases exclusively from the point of view of the practice of medicine.

Dr. Cole continued to write on this subject, and in a paper published in 1928 (12) he wrote:

> It must be admitted that the science of medicine has not reached a high state of development, even such as physiology has attained. And furthermore, we must admit that many of the most important contributions to this science have been made by workers in related fields. Nevertheless, I believe that its greatest advancement will come only when it shall be pursued by men whose primary interest is in disease. Important contributions have been made by clinicians, but only comparatively recently have any considerable numbers of physicians become conscious of their obligations to contribute to this science, and only still more recently have physicians been given any relief from the burdens of practice which will give them opportunities for studying disease by scientific methods. It is true that many of the contributors to other branches of science also teach, but the practice of medicine is a much more time- and energy-consuming occupation than is teaching.

It has been only a little more than thirty years since Dr. Cole and Dr. Cohn stated these goals of medicine so clearly and so explicitly, while at the same time describing the conditions existing at the time they wrote. They were writing toward the end of the second decade of what we are calling a transition period, and one can say that by that time the problems had been examined, the goals had been stated, and the machinery had been set in motion for their attainment. I believe that it may fairly be said that, in the thirty years that followed, medicine in America has closely approached and even in some respects attained the level of physiology and of the other nonclinical sciences. Quantitatively one need only think of the numbers of highly-trained young men and women now occupying full-time positions in the various branches of medicine and surgery, distributed through the medical schools and hospitals of the United States, of the membership of the numerous societies devoted to clinical investigation, and of the hundreds or thousands of those who, although not yet elected as members of these special societies, attend their meetings, both national and local. The numbers of such individuals, who were relatively rare when Dr. Cole and Dr. Cohn wrote, must now be very near the total of those engaged in teaching and research in physiology, even when the latter is interpreted to include the cognate sciences of biochemistry and pharmacology.

Qualitatively, there is sufficient evidence in the programs of these special societies and in the papers in such journals as the *Journal of Clinical Investigation*, which was the pioneer, and the many other journals that publish the results of research devoted to medicine to make it very clear that such research in America is on a very high level indeed. It is of interest to note that there has been an evolution in the concept of clinical investigation. When the American Society for the Advancement of Clinical Investigation was under organization, the prospectus (13) and the presidential address (2) construed clinical investigation as "medical research . . . by men engaged actively in the practice of medicine," and the emphasis was on study of the patient "by the methods of the natural sciences." In publishing the history of the Society, by now called the American Society for Clinical Investigation, in 1949 (13), the Editors of the *Journal* found it necessary to append a letter to the history, in an effort to define "what is and what is not clinical investigation", and arrived at the conclusion that: "Essentially, clinical investigation is the study of the sick person, his past experiences and adaptations, and their relation to his present plight as it is manifest by deviations in structure, function and behavior, and the internal and external processes upon which they depend." Now, a short ten years later, the statement of policy in each issue of the *Journal* reads: "The Journal of Clinical Investigation is designed for the publication of original investigations dealing with *or bearing on* [emphasis supplied] the problems of disease in man, and it is the policy of the editors that the *Journal* should cover the field of clinical investigation in its broadest sense." While the emphasis is still on disease as it occurs in man, the least common denominator of those engaged in clinical investigation appears now to be concern with the diseased state, regardless of whether it is observed in man or produced experimentally in other animals. This is the science of medicine, as envisaged by Alfred E. Cohn in 1927 (11).

To attempt to make a qualitative comparison between present-day publications classified as physiology and those classified as medicine might well lead to invidious distinctions. That Dr. Cole felt free in 1928 to say that medicine had not reached as high a state of development as physiology had attained, while such a statement could not now be defended, gives an indication of the progress of medical science in the intervening time.

One of the outstanding phenomena of recent years has been the growth and development of biochemistry. During my student years, prior to 1910, physiological chemistry, as it was then commonly called, was a relatively simple chemical adjunct to physiology. It consisted largely of applications of organic chemistry, mainly qualitative, to physiological problems. It had not reached the clinic and it had not become quantitative; these developments were to await the contributions of Van Slyke, Folin, Benedict, and others to methodology; they did not come into full flower until the publication of Peters and Van Slyke's *Quantitative Clinical Chemistry*, in 1931–32. It is hardly necessary here to attempt to describe present-day biochemistry. It is of interest, however, to note the degree to which clinical investigation, as of now, derives from biochemistry. Again, this development has not been to the detriment of biochemistry as an independent science. Biochemistry, apart from medicine, continues to grow apace, as do both physiology and medicine.

I have dwelt here on the part I played in the development of the clinical departments at the University of Chicago. Again there arises the question, as it did in connection with Peking, as to what my varied duties and preoccupations did to the scientific part of my personality. I have noted, in the case of the Peking episode, that I was kept alive scientifically by my associations with Van Slyke, Henderson, Alfred Cohn, and others. I began my stay in Chicago under the theory that I was to continue actively as Professor of Medicine and that the activities incident to building, organization, and administration were temporary. While the buildings were being erected I did, in fact, find it possible to spend a winter at the Rockefeller Hospital and another with Friedrich von Mueller in Munich. But on my return to Chicago, and with the growing complexity of the administrative problems, I found myself being more and more involved in them. My correspondence of that period shows that at the time of the dedication ceremonies in 1927 I was already at the point of withdrawing from any professional activities.

For several years I was almost wholly immersed in non-professional work, and devoted myself to a combination of promotion, development, and administration. I was rescued before it was too late by A. Baird Hastings, then a Professor of Biochemistry in the Lasker Foundation in the Department of Medicine at the University of Chicago. At his insistence I found it possible to spend some time regularly in his laboratory, and I became interested in the state of calcium in the blood. Hastings and I arrived early at the belief that this problem could be attacked by the use of biological indicators, and we began with the perfused isolated heart of the rabbit—a technique I had learned in Loewi's laboratory twenty years earlier.

By the end of 1932 my administrative career was over, and on January 1, 1933, I transferred to a professorship of pathological physiology in the Department of Physiology, still at the University of Chicago. The full story of this transfer does not belong here; suffice it to say that many of those concerned with the promotion of the new outlook on medicine felt the effects of what amounted to an occupational hazard. In my case this led to the inauguration of a new chapter in my relations to physiology and medicine, and in retrospect it was the best thing that could have happened to me. Perhaps my most difficult accomplishment was a self-imposed re-education in physiology and medicine, necessitated by a long period of preoccupation with non-professional affairs. This, coupled with my investigative activities, at first confined within narrow limits, led to a broadening of my scientific interests, until I found myself concerned with a wide area that until then had been but little cultivated, i.e., the physiology of bone. Except for interruptions for active duty during World War II, assigned to the U. S. Army Chemical Warfare Service, and for other U. S. Government assignments in civilian capacities, my time since 1933 has been devoted almost entirely to this field, with a maximum of time for research and study and with almost no demands on me for teaching or for other departmental duties.

Shortly after my transfer to the Department of Physiology, and partly because Hastings and I had had indifferent success in our attempts to secure quantitative data by use of the isolated rabbit heart, I arrived at the idea that the known sensitivity of the frog's heart to the concentration of calcium in a perfusing medium might be turned to good account for our purposes. Again this was a direct consequence of my previous association with Otto Loewi, by reference to his use of the frog heart for demonstration of the humoral transmission of nerve impulses. This idea led to immediate dividends and was responsible for an extended period of scientific productivity. We were able to demonstrate that the frog's heart responds only to ionized calcium, and that it is not affected by calcium complexed with citrate or in other combinations.

Although Hastings and I were immediately able to make observations of calcium ion concentrations in biological fluids, such as blood serum and cerebrospinal fluid, our first success, from the point of view of quantitative relationships, was the determination of the dissociation constant of the complex of calcium with citric acid. This has subsequently been confirmed, by more conventional methods, with only very small deviations from the values arrived at by us with the frog heart. Our next adventure was with blood serum, and our experience may be worth relating. In spite of the fact that we had just dealt with the dissociation of the calcium-citrate complex, we were still under the influence of the idea, prevalent at the time, that the ionized fraction of calcium in the serum was independent of that known to be associated with protein. We were making observations of the calcium ion concentration in serum, and encountered a sample in which this was above the range of sensitivity of the frog's heart being used. To bring it down to a level at which it could be measured, the serum was diluted with physiological saline, whereupon it became apparent that the calcium ion concentration had not been correspondingly reduced. Other dilutions were made, with similar results. Only after several days of puzzling over this did the obvious reason occur to me, i.e., that the calcium ions and the calcium combined with protein were in equilibrium with each other and that the dilution was bringing out the mass-law effect we had studied with citrate. It then became a simple matter to fit the data to a mass-law equation. The study of this relationship was then extended, and the results were put in the form of a nomogram. This has been accepted very generally as a description of the interrelation between calcium and protein in the serum, and the nomogram has been widely reproduced. The incident is a good illustration of the influence of a fixed idea upon the interpretation of experimental data; we escaped from this trap by a chance observation.

There followed a number of publications, all related to the calcium ions of the blood. Among them were papers relating to the regulation of calcium ion concentrations by the parathyroid glands—still one of my major interests.

In 1935, Hastings having left for Harvard, and the exploitation of the frog heart having reached a point of diminishing returns, I began to turn my attention to the mechanisms of transfer of calcium between blood and bone, a subject which has been and still is of great interest. Again I formed a new association, this time with Dr. William Bloom of the Department of Anatomy, and we formulated our goal as that of bridging some of the gaps between the chemical and morphological approaches to an understanding of calcification and calcified tissues. This led to a further broadening of our interests, and we found ourselves in the midst of a complex system of structure and function, on the macroscopic, microscopic, and submicroscopic levels, with numerous and varied chemical and physiological interrelationships. We realized that these furnish the subject matter of the physiology and biochemistry of bone—a subject matter which we attempted to organize and which we were led to explore in many directions. It would obviously be wrong to imply that we were the first to make such explorations. What we did contribute, I believe, by a systematic approach to this problem—as well as to any substantive additions we may have made to the literature—was to bring some order out of chaos and to stimulate others to work in what had been a neglected field and is now in a period of rapid expansion of interest and of concentrated scientific effort. In this sense, perhaps, Bloom and I were pioneers in the physiology of bone.

My first publication with Bloom appeared as an abstract in *Science* and is dated January 1, 1937. It was on the mode of action of parathyroid extract on bone and reported on the cellular transformations observed under the influence of the parathyroid hormone. It represented mainly the contributions of Bloom, as a cytologist, to a problem in the physiology and pathological physiology of bone, and it was my introduction to this part of the physiology of bone and of the parathyroid glands. We then studied calcification in developing and growing bone, making use of a new procedure, devised by Bloom, for cutting serial sections of the bones of young animals without decalcification. This method later proved of value in the study of deposition of radioactive isotopes in bone and has been widely used for this purpose, both during and since World War II. We then turned our attention to the secondary system of bone that appears in the marrow cavities of the long bones of laying birds—a phenomenon discovered some years ago by Kyes.

During the academic year 1936–37 I was joined by Marshall R. Urist, then newly graduated from the college of the University of Michigan, and there began a new collaboration that has proved very fruitful. Urist first studied calcification in the callus in healing fractures in rats, making use of the sectioning method introduced by Bloom. He is now on the faculty of the University of California at Los Angeles, where he combines active practice and clinical investigation in orthopedic surgery with basic research on the transport of calcium in the blood and on related problems. For more than twenty years we have continued our collaboration and for some years have had the benefit of generous grants from the Josiah Macy, Jr. Foundation, given in support of our joint contributions. Our collaboration has also resulted in the publication of a book which embodies the systematic approach to the physiology of bone (14) that had its root in the joint efforts of Bloom and myself.

The close association with William Bloom continued for some years. The final paper of which we were co-authors was published in 1953. The senior author was M. Heller, and the paper was on cellular transformations in mammalian bone induced by parathyroid extract—the theme of the first paper by Bloom and myself sixteen years earlier. In the same year I was retired to emeritus status but have continued to maintain a laboratory in the Department of Physiology. In recent years my attention has been divided between writing and the laboratory, in both of which I have been aided in large measure by Ann M. Budy, who has been my research associate for some years. The work that has appeared from my laboratory during the past decade on the effects of estrogens on the bones of mice and rats is mainly attributable to her. These are the only two mammalian species so far discovered that exhibit a specific skeletal response to the female sex hormones, and their study has added an interesting chapter to the physiology of bone. In addition to our own writing we have been called upon with increasing frequency to give editorial advice and assistance to others, both before and after submission of manuscripts for publication. This has been time-consuming, but a rewarding use of energy.

After World War II, and beginning in 1946, I participated in the Macy Conference on Metabolic Aspects of Convalescence. This later became the Conference on Metabolic Interrelations and was terminated in 1953. It had an important influence on the growth of interest in the physiology of bone and was succeeded by the Gordon Research Conference on the Chemistry, Physiology, and Structure of Bones and Teeth. This, in turn, has grown to a point at which it taxes the facilities available to it and is a measure of the expansion of interest from the few individuals who took part in the early Macy Conferences to the hundreds now engaged in the study of calcified tissues. This interest has also led to numerous other conferences on related topics. Perhaps bone will eventually find a place for itself in the standard textbooks of physiology!

I like to think of my own professional life, covering the past fifty years, as divided between two periods. During the first period, which ended in 1932, much of my thought and energy went into my participation in the establishment of two institutions—Peking and Chicago. At intervals I was able to give time and thought to research in medicine and physiology. I came under the influence of some of the leaders in the medical sciences and of the movement that characterized the transition period about which I am writing. In addition to those I have mentioned as my teachers as a medical student at the University of Chicago, upon some of whom, notably Carlson, I continued to lean, I may mention, not necessarily in the order of their importance: Otto Loewi, Rufus Cole, Alfred E. Cohn, Donald D. Van Slyke, Simon Flexner, Abraham Flexner, Jacques Loeb, P. A. Levene, William H. Welch, L. J. Henderson, and Friedrich von Mueller. From these, among others, my scientific heritage derives. This period in American physiology and medicine produced many outstanding figures, and in one way or another I came in contact with a large number of them.

The second period, for me, began in 1933 when I left administration and clinical medicine for physiology. In the quarter-century since then, and beginning when I was already forty-five years of age, I made a fresh start and established myself in a new and growing field of medical science. Those with whom I have associated since then, many of whom have been co-workers, are legion. From many I have derived stimulation, encouragement, and support. In connection with my contributions to the physiology of bone and to its recognition as a field of scientific endeavor, there have been two high points in recent years. In 1957 I received the degree of M.D., *honoris causa*, from the University of Lund, Sweden. This is the same university from which A. J. Carlson and Otto Folin, both of Swedish birth, received the same degree in 1919, on the occasion of the 250th anniversary of the founding of the university. In 1959 I was made an honorary member of the American Academy of Orthopedic Surgeons, a distinction which I value highly.

During my earlier period I thought of myself as in preparation for an academic post in internal medicine. This was before the era of American Boards, and I was free to make of myself what I would, without a prescribed course of training. As revealed by my publications during this time, it appears that even then my leanings were toward physiology rather than toward medicine as the science of disease. Most of what I published would be classified as physiology, some of it pathological; my contributions to medicine, as such, seem to have been incidental to those to physiology. During my later period the distinction becomes even more marked. Such contributions as I have made to the pathology of bone, or to the clinical features of diseases of the skeleton, are in the realm of pathological physiology. I recall that while I still considered myself as in training for internal medicine I rationalized my interest in such problems as the chloride shift in blood, which led me to L. J. Henderson, by saying that this fundamental knowledge was essential to a subsequent study of a diseased state, such as edema. As of now, I would say that it was the fundamental problem that really held my interest. To judge from the papers that are currently published in such journals as the *Journal of Clinical Investigation,* I believe that this is true also of many investigators who are in training or who hold positions in departments representing the clinical branches of medicine.

In my experimental work I have adhered to relatively simple methodology. Harry Murray and I did our work in L. J. Henderson's laboratory with a minimum of facilities and of equipment. We adapted a galvanized iron washtub for use as a constant temperature bath, with a primitive thermoregulator. Tonometers were not then available, and we made one out of a wide-mouthed reagent bottle. The later contributions to the state of calcium in the fluids of the body depended upon a frog heart, a heart lever, and a kymograph with a smoked drum. The work in Peking, with Van Slyke and Wu, was done mainly with glassware brought there by hand by Van Slyke. Methodology has become much more complicated since those days, and for much of this I must rely upon others. So far as my personal contributions are concerned, I am still carrying on in the tradition of my first teacher—A. J. Carlson.

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