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# MEDICAL RESEARCH IN THE CLINIC AND LABORATORY[1]

By Dr. SIMON FLEXNER

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IT gives me very particular pleasure to address you —the graduating class, the trustees and faculty of this great institution—on an occasion which promises to be historic in the annals of medical education in the United States. Perhaps I may add that I feel highly honored, not only in having been invited to address you, but because of the close association in space of this institution and the Rockefeller Institute which immediately adjoins it to the south. I feel that I may take pride, which I hope is pardonable, in having had a very small share in determining the location of the New York Hospital and Cornell Medical College on its East River site.

I recall with great pleasure and satisfaction those early visits to the Rockefeller Institute of Mr. Edward W. Sheldon, the president of the New York Hospital, and Mr. Payne Whitney, a great benefactor, to discuss the question of site, and my eagerness that they should choose the particular one on which this monumental building now stands. It is true that the site then considered was far less extensive than the one ultimately assembled, but that is an unimportant detail. What is significant is that your splendid institution and the Rockefeller Institute should have become close neighbors and that they may come to react on each other in a manner to insure the realization of the main object for which they have been founded, that is, the advancement of the science of medicine in its many aspects.

May I say that I am so circumstanced that I can now glance backwards over a forty-year stretch of time during which medical education in this country has progressed with constantly increasing speed? It happens that I entered the Johns Hopkins Hospital

[1] Commencement address, New York Hospital—Cornell Medical College Association, June 8, 1933.

in the year 1890. The hospital itself had just got under way; the instruction in pathology and bacteriology was, in a sense, the sole university course given in the institution. That was three years before the formal opening of the medical school whose history was to prove so significant for medical education in the United States.

Do not mistake me: there had already been excellent teaching of medicine in the United States. But the Hopkins experiment was an innovation. Like all such things, it had a history, part of which was the visit of Thomas H. Huxley to Baltimore in September, 1876, and his outline of a modern medical curriculum; part was the appointment of Dr. William H. Welch in 1884 as professor of pathology in the university; and part was the courage of two women—President M. Carey Thomas, of Bryn Mawr College, and Miss Mary E. Garrett, of Baltimore—who with other women raised a fund making possible the opening of the school, and laid down conditions, then regarded as revolutionary to a high degree and to-day commonplaces of educational practise, prescribing a college degree, proficiency in the sciences and modern languages, and coeducation as the requirements for entrance on studies leading to the medical degree.

The revolution consists not in the innovation alone —that might readily have been superseded—but in the wide adoption of the principles of educational policy involved. In essence, this change from the old order was the recognition of the claims of science in medical education as a prime object of attainment. To-day we recognize widely that the pursuit of knowledge is not, indeed can not be, divorced from the teaching and practise of medicine. I hasten now to add that in the term "practise of medicine" I do not divorce clinical from laboratory medicine. Rather I hold that they are two sides of the same medal—a precious thing—which can never be divided in fact, as long as medicine as a profession actually lives.

There is, of course, no particular kind of knowledge which is superior to another, just as there is no division between knowledge gained by those who do and those who do not apply that knowledge in practise. So long as it is knowledge with which we are dealing, it is science; and science is one thing, not two. The only distinction to be noted between what may be called "clinical" as opposed to "laboratory" science is that the former is more difficult to attain. But that it can be attained, the history of three hundred years of investigation by experimental means amply shows. I see, therefore, in the organization of this great medical institution, which may quickly become a model for the world, recognition of the equal claims of the laboratory and the clinical scientist. Now, every laboratory worker is not merely an abstract scientist; many are on the very borders, indeed even within those borders, of clinical medicine; just as many clinical investigators are similarly placed with respect to the laboratory. This is as it should be; and I believe the crossing of these borders should be promoted in every feasible and advantageous way. In this manner, as much as or even more than in any other, can this great association express its faith in the ideals on which it is founded, and help to realize the future, which promises increased brilliancy, of medical science and practise in this country.

That the faculty of a medical college contributes to the advancement of science is, of course, a truism. It is not always recalled that a remarkable part of the growth of scientific medicine has come from the labors of practical men. By "practical men" I mean men who are engaged in the practise of their profession, besides which they find the time to respond to those uncontrollable impulses of guided curiosity to explore nature. I like to recall that gallant spirit, Dr. Samuel J. Meltzer, known to all the older teachers present here, who amid an exacting practise in New York regularly produced significant contributions to knowledge in the domains of physiology, pathology and clinical medicine.

But the most famous example of all time is William Harvey, a physician engaged throughout his life in a multiplicity of practical exploits, who yet found time to make the epochal discoveries attached to his name, which are the foundations of present-day physiology and embryology. Of this great man it has been said that his discovery of the circulation of the blood stands to medical practise in much the same relation as the discovery of the mariner's compass stands to navigation. Let us pause a moment to recall the salient facts of this discovery.

Harvey's epochal book was published in 1628. It seems probable that he began teaching his doctrines to his classes as early as 1616—the year of Shakespeare's death. For more than ten years, Harvey delayed any formal publication of his experiments and deductions, meanwhile inviting criticism and opposition to his views from all sources, in order that the complete truth, free from any falsities and misconceptions, might be disclosed. To-day, as it did then, his modest treatise stands as a landmark in human history, and a perusal of the methods of experiment employed and the mode of presentation adopted arouses feelings only of admiration and emulation.[2] The fundamental thesis of Harvey's teaching is expressed in almost winged words by a modern physiologist: that only by searching out and studying the secrets of nature by way of experiments can we hope to attain in the words of Job "to a comprehension of the wisdom of

[2] W. Harvey, "Motion of the Heart and Blood in Animals." Everyman's Library, 1906.

the body and the understanding of the heart,"[3] and thereby gain that mastery of disease and pain which will enable us to relieve the burden of mankind.

The announcement of the discovery produced a sensation; it was opposed, but not by the younger physicians. Something of present-day prejudice, fortunately diminishing rapidly, can be discerned in the fact that Harvey's medical practise fell off. Patients feared to put themselves under the care of one accused by the ignorant and envious of being crack-brained and of putting out new-fangled and dangerous doctrines. There was fortunately one man in a high place who showed lively interest in the discovery. Charles I supported Harvey and appointed him his personal physician.

If we penetrate a little farther into the genesis of Harvey's discovery, we may receive enlightenment and encouragement to-day. It was in Italy that Harvey came into relation with the scientific spirit of the age; indeed, the two independent geniuses, Galileo and Harvey, whose labors determined unexampled progress in the physical and biological sciences, were for a time contemporaries at the University of Padua.

It is a short step, only about half a century, from the astounding figure of Harvey to that of the overwhelming figure of Newton—the "lawgiver of the universe," in the phrase of his contemporaries. I venture to join these two men's names because they represent in truest measure the scientific spirit. Both men were enemies of mere speculation and upholders of the experimental method, and both were conspicuous by reason of the extreme caution with which they promulgated their discoveries. Newton, even less than Harvey, was possessed of the passion, verging on fanaticism, for mere scientific discovery which has distinguished many men. He had almost to be cajoled into the enunciation of the discovery of the law of gravitation, and he all but failed to complete the "Principia," because he detested controversy.

"I see I have made myself a slave to philosophy; I will resolutely bid adieu to it eternally, except what I do for my private satisfaction, or leave to come out after me; for I see a man must either resolve to put out nothing new, or become a slave to defend it."

It is not always appreciated that science is logical. The progression of discoveries is something not to be predicted often, but always to be explained. What seems, at times, to be the most revolutionary, because unexpected, discovery, is not so in fact. There is a thread of gold, as it were, running through and uniting all discovery; and there is even a connection, not always at once apparent, between discovery in the physical and in the biological sciences. This interrelation of all phenomena is becoming more and more impressive as scientific knowledge grows by leaps and bounds. And hence you will see in this center of medical activities, devotees, if I may use the term, of the physical as well as the biological sciences, and this not only in the laboratory, but also in the clinic, where more and more chemical and physical concepts and methods are being introduced into practise.

I remarked that science is logical. It may interest us to consider the testimony on this subject of great men in science. Newton is reported to have said that if the men of his generation saw further than their predecessors, it was because they stood on the shoulders of giants. Now, the giants of whom Newton was thinking were Copernicus, Tycho Brahé, Kepler, Galileo and Descartes. Just the other day, I found that this felicitous statement had been made in essence some four hundred years earlier, that is, in the twelfth century, by a lovable scholar, Bernard of Chartres, who said: "In comparison with the ancients, we are like dwarfs sitting on the shoulders of giants." The giants in this instance were doubtless the early Christian Fathers.

The idea of succession of scientific events and metaphors to describe them have impressed themselves on the greatest minds. In that enlightening book, "An Introduction to the Study of Experimental Medicine,"[4] recently made available in an English translation, Claude Bernard states:

> Each great man belongs to his time and can come only at the proper moment, in the sense that there is a necessary and ordered sequence in the appearance of scientific discoveries. Great men may be compared to torches shining at long intervals to guide the advance of science. They light up their time, either by discovering unexpected, fertile phenomena which open new paths and reveal unknown horizons, or by generalizing acquired scientific facts and disclosing truths which their predecessors had not perceived. If each great man makes the science which he vitalizes take a long step forward, he never presumes to fix its final boundaries, and he is destined to be outdistanced and left behind by the progress of successive generations. Great men have been compared to giants upon whose shoulders pygmies have climbed, who nevertheless see further than they. This simply means science makes progress subsequently to the appearance of great men, and precisely because of their influence. The result is that their successors know many more scientific facts than the great men themselves knew in their day. But a great man is, none the less, still a great man, that is to say—a giant.

It may be profitable to pursue this line of thought a little farther. One of Leonardo da Vinci's aphorisms was that truth is always the daughter of her period. We see this belief expressed in the oft-

[3] E. Starling. *Lancet*, 1923, ii, 869.

[4] Claude Bernard, "An Introduction to the Study of Experimental Medicine," English Translation, p. 41. The Macmillan Company, New York, 1927.

quoted phrase of Pasteur relating to the "prepared mind." What was meant here is that discovery comes to minds so fortified by accurate training as to be alert to perceive and quick to seize upon the novel and essential, which is turned at once to new and unexpected uses. "There is nothing new under the sun," and so it is with this favorite expression of Pasteur. In his use of it, he was merely expressing, perhaps unconsciously, the words which his great countryman Lagrange applied to Newton, "Such accidents only meet persons who deserve them," an expression which is quoted in a letter of the Scandinavian astronomer Hansteen, who wrote to Faraday in 1857 complimenting him on the discovery of electromagnetism.

There is, therefore, a kind of compulsion in science which determines its direction. Hence it happens that a discovery due to be made may be accomplished simultaneously by several independent investigators. The famous instance of this kind is the discovery of oxygen in England by Priestley, in France by Lavoisier and in Sweden by Scheele. Some discoveries are made out of time and must be rediscovered, perhaps even more than once. We have such an example in medicine; it chances to be an example of very great importance in theoretical and in practical medicine. The phenomenon of anaphylaxis, or increased sensitivity of the body to certain chemicals, in opposition to immunity, which is a state of diminished sensitivity, was probably first observed by Magendie early in the nineteenth century; it was rediscovered twice toward the end of the century, and its nature divined at the beginning of the twentieth century. In Magendie's case, he was engaged in trying on animals all sorts of things, helter-skelter, to ascertain their effects. In this way, he injected a rabbit with egg white, and on repeating the injection some days later he discovered that the egg white, at first harmless, now acted as a violent poison. What was needed before anaphylaxis could be properly understood was a development of the science of immunity, which only began between 1890 and 1900.

The French physiologist Magendie would be immortal if for no other reason than that he discovered Claude Bernard and gave him the opportunity for scientific studies. Nothing could be more impressive than the advance in physiological science in the period of a lifetime made by Claude Bernard through his systematic, imaginative, as well as accurate method of experimentation, in comparison with Magendie's stabs in the dark. Magendie said of himself: "Every one is fond of comparing himself to something great and grandiose, as Louis XIV likened himself to the sun, and others have had similar similes. I am more humble. I am a mere street scavenger of science. With my hook in my hand and my basket on my back, I go about the streets of science, collecting what I find."[5] Compare this capricious search for knowledge with the amazingly thoughtful, incisive experiments of Bernard, who, among many other epochal discoveries, gave us the first proof of internal secretion and the name which we still employ in endocrinology.

Among investigators, the rarest are those men with a presentiment of new truths; the far greater number merely develop and follow the ideas of others. In a few instances the presentiment is extraordinary, but it is always likely to be a brilliant example of the scientific use of the imagination. We must ever keep in mind that the outstanding discoveries in science are the accomplishments of real men and usually of great men. Now, as it has been well said, great men are just those who bring with them new ideas and destroy errors. They do not, therefore, respect the authority of their predecessors, and they do not move in an ordered way. While it is, of course, true that the discoveries of the great men preceding them stand at the base of their own discoveries, yet neither one nor the other is ever the promoter of absolute and immutable truths.[4]

If now we turn back to our own profession, it may be said that we have learned that there is no sharp line between health and disease, and no sharp distinction between the functions called physiological and pathological. A knowledge of the body will include all the biological processes with which we can deal. The animal body has often been compared to a watch, and the physician to the expert watchmaker, and it has been hoped that in due time doctors will be as good at their craft as watchmakers are at theirs. It is true, of course, as John Brown, the gifted author of "Rab and his Friends," has pointed out, that the watchmaker is not called on to mend the watch while it is going, and that this makes all the difference. But the simile is far more imperfect than this, since the most cunning of Swiss watches, which tolls the precise minute of the day or night, shows the day of the month, the quarters of the moon, and even other successive events, is so far simpler than the beautifully constructed and ingeniously integrated animal body that it is almost an offense to compare one with the other.

It is precisely this recognition of the multiplicity of the forces which control on the one hand the body in health and, on the other, those diversions which produce disease, that characterizes present-day medicine. Much of medical research, whether in the clinic

[5] Michael Foster, "Claude Bernard," "Masters of Medicine," p. 40, 1899.

or the laboratory, concerns itself with the detection and estimation of the power of these forces, and the means by which they may be controlled. We have thus witnessed the rise, not only of a chemistry or, if you will, a physics, as well as a biology of disease, but we are witnessing a spirited study of the underlying factors of constitution as affecting the health or the disease of individuals and of larger units or communities. Medicine, therefore, takes on an almost universal aspect; it is properly considered the most inclusive of the sciences and the most complex of the arts.

But the search for knowledge of the underlying conditions determining health on the one side and disease on the other is no longer confined to man himself. While he is the main object of our pursuit, he is by no means the only or even the chief object which is being investigated. Just as Francis Bacon announced that he proposed to take all knowledge for his province, so does the medical investigator to-day take all animated nature as his legitimate field of exploration. There are no closed compartments in nature into which man, animals and plants can be separately placed. All are related organically and, as we may say, united physiologically and pathologically. No essential biological division exists between man and the lower animals and plants, whether in respect to health or to disease. If, therefore, we would learn, and through learning grow more powerful and effective to prevent and to cure disease, to lengthen life and to increase happiness through security in all its varied forms, then we should endeavor to advance in biological knowledge, which alone can free us still further from the evils of disease.

To the members of the graduating class I offer my sincere felicitations and my wish that they may carry the spirit of the student into whatever branch of medicine they elect to follow. After all, it is the spirit which matters. The college sends you out with high hopes; may your own ambitions realize them.

# THE STORY OF ISOTOPES[1]

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THE story of isotopes is not a long one in time for it is practically all comprised within the past quarter of a century, but it presents many points of great general interest. The idea that atoms of the same element could differ in mass was repugnant to chemists and when, about 1910, Soddy proposed that the newly discovered data of radioactivity led inevitably to the possibility of leads occurring of different atomic weights but of identical chemical properties, he received much hostile criticism. The examination of naturally occurring leads by those who had the best reason to doubt the theory, the specialists in atomic weights, showed in due course that Soddy was right.

It is remarkable that the extension of the theory to the non-radioactive elements should have followed so closely, for this depended on a technical advance in methods of analysis of rays of charged atoms which had little or no relation to the discovery of radioactivity. Sir J. J. Thomson's parabola method of positive ray analysis suggested the probability of the inert gas neon being complex and an account of a partial separation of its isotopes was published in 1913, but the first definite proof of the general occurrence of complex elements composed of atoms of whole number mass was given by the mass-spectrograph in 1919. Chicago is closely associated with the early work on isotopes by the well-known researches of Harkins and Dempster. The latter announced the first analysis of a metallic element, magnesium, in 1920.

Aided by its focusing property the first mass-spectrograph had a resolving power sufficient for any element up to the rare earth group, and an accuracy of measurement of about 1 in 1000. During continuous use from 1919 to 1925 it was successfully applied to over 50 elements, the whole number rule was well established and the divergence of hydrogen from this roughly measured. Other slighter divergences were indicated but greater accuracy was required. In this connection one must not omit to note the work of the American Costa, who set up a mass-spectrograph in Paris and in 1925 published comparisons of some light atoms of an accuracy of 1 in 3000.

In the same year the original mass-spectrograph at the Cavendish Laboratory was replaced by a second one having double the resolving power and capable of comparing masses with an accuracy of 1 in 10,000. By means of this work was extended to heavier elements and a large number of new isotopes were discovered. Its high accuracy enabled the divergences from the whole number rule to be measured in many atoms. These expressed as "packing fractions" were found to lie on an interesting curve which has been used by Millikan and others for theoretical purposes. One of the most interesting discoveries made with the second mass-spectrograph was that uranium lead con-

[1] Abstract of an address before the General Session of the Century of Progress Meeting of the American Association for the Advancement of Science, Chicago, June 21, 1933.