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CLINICAL INVESTIGATION[1]

By Dr. GEORGE R. MINOT

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WE are here to-day to celebrate the opening of the Squibb Institute for Medical Research, which stands as a fitting tribute to Edward Robinson Squibb, the founder of this distinguished pharmaceutical organization. Dr. Squibb was an eminent physician and chemist and his name has become synonymous with certain ideals in medicine and pharmacy. The scientist's love for truth, so marked in him, and the painstaking and conscientious care of every detail of his activities led him to never neglect research and general scientific work, which he recognized as essential. Dr. Squibb's services to the army and navy, especially during the Civil War, were most significant, for he supplied them with highly dependable medical supplies and particularly anesthetics. His master formula was honor, integrity and trustworthiness. His work was such that no contemporary had to consider writing such a book as Christopher Merrett wrote in 1669 with the title, "A Short View of the Frauds and Abuses committed by Apothecaries; as well in Relation to Patients, as Physicians: and the only Remedy thereof by Physicians making their own Medicines." Dr. Squibb's published investigative studies extended from 1855 to 1900, in which year he died at the age of eighty-one. The studies concern especially the production and preparation of therapeutic substances which the physician prescribes and which must in final analysis be tested on human beings for their exact action and value—a form of clinical investigation.

It is a physician who undertakes clinical investigation, and I plan to consider a few general aspects concerning this subject especially as referable to the physician and patient.

[1] Presented at the dedication exercises of the Squibb Institute for Medical Research, New Brunswick, N. J., on October 11, 1938.

Doctors deal with human problems, and to solve them an active creative imagination and scientific curiosity are necessary tools. Every patient who consults a doctor presents a problem for investigation before the best advice can be offered. There is nowhere that a patient stands so good a chance of being benefited as in a clinic where his disease is arousing scientific curiosity. A studious inquiry of sick people is what every good practitioner makes daily. At the bedside he must constantly sharpen his powers of observation and judgment and recognize that his education is never ended but must be continued by his own strenuous mental effort. Any doctor should appreciate the spirit and understand the principles of research and develop an investigative habit of mind. His curiosity to learn must never wane, for if it does he soon will become inefficient. Since medicine deals so essentially with human problems the physician must constantly strive to broaden his outlook on life. This may be done by cultivating interests that often would be considered far removed from the practice of medicine, such as some aspects of natural history or art. These various attributes of a physician must be applied at the bedside in the elucidation of the phenomena of disease. There is no sharp line of demarcation between the practicing physician and the physician who makes it one of his duties to conduct clinical investigation. Indeed the best sort of properly trained clinical investigator must be an able clinician, one who understands human beings and can act wisely for all aspects of a given individual. His training in investigative principles must be sound, and he should have an ardent desire to seek for knowledge by scientific methods. In other words, he must wish to carry the torch forward so that the oncoming generation of physicians will find it nearer the ultimate goal.

Clinical investigation may be pursued in institutions designed only for that purpose or in any hospital. It may also be undertaken wherever the physician has his headquarters if he trains himself to keep in mind the study of problems. The establishment of appropriate space and opportunities for clinical investigation in large hospitals where the study of patients under controlled conditions can be undertaken seems especially wise. This permits investigators to be surrounded with a wealth of clinical material for study from which ideas can originate and allows the hospital to be a progressive modern institution and the patients to receive the very best treatment. It is of great advantage if the clinical investigator is in close contact with men working in a wide variety of scientific fields and especially in those disciplines closely related to clinical medicine, such as pharmacology, bacteriology, chemistry and biology, as you have here in this institute. Mingling of such men offers opportunity for the free exchange of thought which can lead to beneficial results. Indeed this arrangement allows the ideas originating from the needs of the patient to be readily carried for elucidation to some laboratory of fundamental science, and knowledge obtained there to be applied in the clinic. For the cure and prevention of disease and the relief of pain the final test is on man himself, so that a clinical investigative unit need be a part of, or associated with, an institute for medical research. The director of this institute, Dr. Harrop, certainly appreciates this, if for no other reason than because of his well-recognized accomplishments in the fields of experimental medicine and clinical investigation, which make advances hand in hand. I am delighted to learn that clinical facilities with a small ward for the observation of patients in connection with various problems being studied by the research staff are being planned.

Clinical investigation does not necessarily require great laboratory set-ups. The sick individual is the center of the picture, so that wards with patients are the salient feature of the clinical investigative unit. Clinical investigations frequently are suggested from individual patients' problems, and these may concern matters removed some distance from the patient himself. Indeed, clinical investigation may necessitate pursuit at a distance from the investigator's headquarters or institute because the solution of problems may be found, for example, in the physical, biological or social aspects of a patient's community or home. The technical apparatus required for intelligent observations and for the proper care of the patient is but a means to an end and is a relatively insignificant, though often to the casual observer the most impressive, feature of a clinical investigative unit. The most important and significant possession, besides the sick people, is the recorded data collected with a view to obtaining a definite pattern and often ascertained by simple procedures, frequently entirely by the use of the intellect. It is from the trustworthy records of natural phenomena and of the actions of organisms under controlled experimental conditions that concepts concerning disease are formulated leading to the alleviation of man's ailments and to knowledge of intrinsic scientific interest. The plodding worker often obtains a long record and masses of data which are sometimes thought to be an indication of good work. That is often far from the case, because the data recorded may have been obtained without critical understanding. Quantity does not supplant quality. The individual with an aggressive inquiring mind can often by skilfully planned questions and observations in relatively small quantity elicit more significant information than is found in some voluminous records. Thus the foundation of research work lies in the quality of the minds of the investigators and the freedom and tranquility permitted for the

use of their abilities. Free choice of problems and free choice to follow leads disclosed must be the privilege of the experienced investigator.

Although any physician may conduct clinical investigation and share his knowledge with his colleagues, the term clinical investigator is usually applied to a man who devotes a considerable amount of time to the study of clinical problems in organized clinical laboratories. Many men who essentially never observe a patient work in numerous fields of science studying problems pertaining to the clinic, but such individuals are not clinical investigators.

A trained clinical investigator may approach problems, broadly speaking, in two different ways. In the first instance an experienced clinician seeks tools through which to solve problems that originate in his mind at the bedside; for example, the man who appreciates that to supply the deficiency of the blood-clotting mechanism in hemophilia chemical procedures should be utilized in an effort to discover something that might permanently alleviate the patient if given by injection each day. The second method of approach is also for a man with clinical training, but one who has acquired the use of tools, to take them to the bedside to apply them to problems suggested by the tools; for example, a man trained in chemistry and especially in the chemicophysical aspects of the clotting of blood, who seeks a patient to elucidate the mechanism of blood coagulation. The former is more truly the clinical investigator, and it is by the intellectual rather than by the technical method that he approaches problems, concerning sick individuals. This does not imply that it is unwise for investigations of fundamental importance to proceed from purely morphological, chemical or physiological motivations without reference to the immediate needs of the clinic, for it is by the study of fundamental problems that most significant advances are made. Both types of clinical investigators have their place in the development of useful knowledge, but if aggregations of individuals, chosen only because they are acquainted with special techniques, form the personnel of a clinical investigative unit the practical needs of clinical medicine are apt to be forgotten.

It is certainly an incorrect conception of research that it makes a man heartless, unsympathetic or indifferent to human suffering. Indeed, many able clinicians who have spent much time in investigation are unusually keen in their ability to appreciate and to treat wisely the anxieties and emotional disturbances of patients. In reality the clinical investigator is apt to be successful somewhat in proportion to his appreciation of the sick man as an individual. He is usually one who has some inborn quality which fits him for an earnest search for knowledge and who by proper training in a suitable environment develops his inquiring abilities. He must have the power to see straight, which is a rare gift. To see no more and no less than is actually before one, to see with one's reason as well as with one's perceptions—that is to be an observer and to read the book of nature aright. To note the resemblances of things one to another may be an essential point in acquiring information. Factors often need study one at a time, yet it must not be forgotten that synthesis is essential in the formulation of final knowledge. The investigator must ponder on topics where emotions blend with cold reason and where the answer is dictated by the emotions, though it is largely formed by reason. Emotion is the driving force that arouses inquisitiveness, sustains interest and keeps the investigator at work through drudgery. Reason is the critical control that guides and checks progress. It is developed by long training in the scientific method. Emotion and reason are always mixed; one can only do one's best to use each for its serviceable purpose and avoid the usual mistake of allowing emotions to dominate one's judgment.

The problem of whether a man is to undertake clinical investigative work does not depend on his precise occupation but lies in the man himself. He who undertakes clinical investigation, however, must learn to recognize clinical facts, realize that intuition often guides and that the patient's health must never be jeopardized. He must establish a detailed diagnosis without pothering over unessential details and proceed to action for every aspect of the patient and his case. Anything studied faithfully develops the mind. Thus, besides what is gained by investigative work itself, this type of work has great educational value. Every physician must be trained to look at problems from more than one angle and be unwilling to confine himself to standardized procedures. Throughout life the physician must keep abreast of the times and, by making frequent contacts with those especially studying medical problems, he will constantly imbibe knowledge. An understanding of the principles of scientific investigation aids him to judge critically, to appreciate the nature and significance of proper controls, and to evaluate the significance of the many communications published on medical topics.

Before a problem is intensively studied it is essential to become acquainted with previously acquired knowledge on the subject. Although subservience to the past makes stagnation, development of it is true progress. Science may render that which went before obsolete, but it builds upon the past, constantly advancing new knowledge from the standpoint of the already known. Thus the investigator must consult authorities in large part by going to the library. Consulting colleagues is extremely helpful but does not alone take the place of reading what has been written on a subject. Conversation alone as the only basis for obtaining information

can lead to confusion between "authority and the oracle," which is perilous to scientific work. A library is not merely a hall of books but a hall of records of human experience and thought, where one may learn the path along which man has toiled and may discover guiding and liberating influences for the future.

Clinical investigation takes a variety of forms. The aim should be to undertake fundamental problems and to appreciate that progress in the clinic often owes its origin to the fields of pure science. The studies are often of a collective nature, as in the evaluation of clinical data, the evaluation of new procedures or in the correlations of chemical and pathologic information. Proper statistical methods must be employed and standard deviations and probable errors calculated. The descriptive discipline of nosography—the painting of accurate pictures of disease—is a useful guide to keep experimental procedures from going astray. This type of work may depend on the good fortune of observing several cases and not on planned investigation. There is need for more accurate work of this sort especially concerning initial symptoms and the natural history of long-lasting chronic conditions. Controlled observations of human pathologic physiology is the nature of many of the studies of the clinical investigator. The question of the origin or cause of disease is of unusual importance to study. Therapeutics, which is linked with pharmacology, is essentially an experimental science and will always have experimentation on man for its chief basis. The action of drugs always needs evaluation. The object, however, is to study the human body and not drugs *per se,* and one method of doing so systematically is by means of its reaction to chemical and physical agents.

The control of experimental conditions in human beings is crude as compared to the utmost rigidity in the control of the worker in pure science, so that data of observations may be only qualitative or but crudely quantitative. One of the many variable factors is dependent on the fact that the human being has a soul and highly organized nervous system. His emotional reactions, worries, jealousies and the like and his reactions to one or more persons can not only lead to illness but affect the functions of organs. The medical-social, psychological, economic and allied aspects of individuals can be investigated with profit. The field is a difficult one for reliable scientific study, because it involves all the complexities of human life. Even so, a considerable fraction of the successful care and treatment of patients and the prevention of much illness is to be identified with the proper consideration of their medical-social problems. A list of the studies a clinician may pursue is of little value. It is more significant to realize that a prepared mind, well-planned scientific observations and the taking of infinite pains will lead to success, and that important original contributions often are made which require only simple technique and clinical wisdom.

The clinical investigator in his search for truth is not to be thought of as a lone worker or as a man sharply separated from other types of doctors. A close relationship with practitioners, specialists, pure laboratory investigators of many types is mutually beneficial. The men in this institute, like investigators elsewhere, naturally realize that assistance may be obtained from a wide variety of divergent sources and that science is not bounded by the walls of any one institution. There are no sharp lines of demarcation between one medical interest and another or between medicine and a variety of disciplines. Cross-fertilization at the border lines of knowledge can serve to develop new information. The advancement of learning can not be made in water-tight compartments. Modern developments have permitted team work in scientific fields to be much more general and prolific where before isolated efforts were the rule. Cooperative investigations between physicians, scientists and all types of scholars trained in different ways as well as between men in different institutions can enhance knowledge concerning the treatment and prevention of disease and the happiness and progress of a people. Such cooperation when spontaneous is fruitful, but when compelled it may be sterile.

More fundamental than the actual discoveries being made to-day is the preservation of the right to engage in research. If all governments, races and individuals would hold the same high ethical view-point of life that Dr. Squibb did, there would be no murmurings of intolerance to intellectual freedom. Security and happiness have profound beneficial effects on the character of intellectual work. As time passes by we must always be alert to adapt ourselves to changes and realize that to understand the present we must look both towards the past and towards the future.

BIOLOGY AND INDUSTRY IN COOPERATION[1]

By Professor AUGUST KROGH

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IT is a great pleasure as well as a great honor to assist at the inauguration of these laboratories, which represent a very important step forward in the ever closer cooperation between biological science and biotechnical industry.

[1] Presented at the dedication exercises of the Squibb Institute for Medical Research, New Brunswick, N. J., on October 11, 1938.