The Clinical Pathologist in RESEARCH

Selections from an address delivered by Harold L. Stewart, M.D., at the Joint Annual Meeting of the American Society of Clinical Pathologists and the College of American Pathologists, on October 3, 1957, in New Orleans.

PATHOLOGY may be defined as the study of disease, not merely the study of body fluids and of abnormal morphology. The pursuit of pathology, therefore, includes research and investigation. The clinical pathologist throughout his entire career in a hospital laboratory is asked to advise on and to participate in research problems, and to interpret the results of research done by others. During his board training the resident pathologist needs to familiarize himself with the methods of experimentation as well as with the broad principles of pathology. How can the clinical pathologist evaluate the results of research by others if he himself has had no instruction in research methods and no actual training or experience in

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The Ward Burdick award for 1957, given annually for outstanding service in pathology, has been presented to Dr. Harold L. Stewart, chief of pathology, National Cancer Institute, and chief of the Pathologic Anatomy Branch, Clinical Center, National Institutes of Health, Public Health Service. The presentation was made October 1, 1957, at the Joint Annual Meeting of the American Society of Clinical Pathologists and the College of American Pathologists in New Orleans.

Dr. Stewart, an authority on cancer of the gastrointestinal tract, has held office in medical societies including the International Academy of Pathology, the American Society for Experimental Pathology, and the Maryland and Washington, D. C., Societies of Pathologists. He has also been a delegate to a number of international cancer conferences.

The Ward Burdick award is given in honor of the Denver pathologist who founded the American Society of Clinical Pathologists. Dr. Burdick, who died in 1928, was noted for his medical organization work.

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the field? To expect this is to expect a man to be a successful clergyman without having studied theology.

THE PATHOLOGIST has independently led the way to many important discoveries. Witness the history of our knowledge of the function of the pituitary gland. It was Pierre Marie who, in 1896, discovered the role of the anterior lobe of this gland in acromegaly, and it was Benda who found growth to be related to the alpha cells. But this important finding was left for the biochemist and endocrinologist to exploit, chiefly because the pathologist was not skilled in other techniques. Pathology, it has been said, depends upon tools of other disciplines for its research. The pathologist of the recent past leaned heavily on bacteriology and immunology for problems in experimental pathology. Today, the experimental pathologist utilizes chemistry and physics in the study of molecular diseases and he will need to learn many techniques to equip himself to take advantage of the wealth of opportunities that he has for research.

It is safe to predict that in time all the lesions of human beings will have been studied by electron microscopy. Just as our knowledge of lesions first studied by the naked eye was enormously increased by study with the light microscope, so will our present knowledge of the histopathology of these lesions be expanded by the resolving powers of the electron microscope. No one is better qualified than the clinical pathologist to study pathological lesions by electron microscopy. He is not just a microscopist seeing particles whose significance he is unable to interpret but is one widely familiar with the morphology and biology of disease.

The "mitochondria" revealed by the electron microscope and the mitochondria isolated by the biochemist in differential centrifugation, which are hailed as something new and strange, were discovered in Leipzig by the pathologist Richard Altmann in 1890 and named in 1898 by the pathologist Benda, who studied them in pathological tissue. The pathologists gave this discovery of mitochondria at once to the biochemist and the cytologist, who believed them to possess and probably to produce most of the cytochrome oxidase and other respiratory enzymes of the cell. Little is known of these organoids in pathological tissue and nothing of their behavior in human tissue. The pathologist should now return to this important field after more than 50 years of neglect.

THE DISCOVERIES that cancer can be induced by X-rays, by tars, and by aromatic polycyclic hydrocarbons led to a great deal of work on carcinogenesis which during the 1940's and thereafter has waned. Today too few pathologists are trained in experimental carcinogenesis. The techniques are not difficult to master. The clinical pathologist already possesses the necessary basic knowledge, including the procedure for a careful autopsy. Almost the only other things he needs to know are the design of the experiments and the methods of preparation of the known or suspected carcinogens for their administration by different routes. . . .

THE FOOD on the American table today in a well-balanced diet of acceptable form may contain many synthetic additives. Some may be toxic and some even carcinogenic for laboratory animals, while other food additives utilized for years past have never been tested adequately for chronic toxicity and cancer-inducing activity. New food additives are being introduced at a rate that precludes careful toxicological testing unless the number of investigators in the field of carcinogenesis be considerably expanded. There is pressing need for experimental research in this field.

THE CHEMIST, the biologist, or the physicist who does research may know his own subject thoroughly, but usually knows nothing whatever about pathology. The pathologist, on the other hand, well trained in anatomical pathology and laboratory medicine, also knows a good deal about chemistry, biology, and physics. Some pathologists have majored in one or another of these subjects, and others hold the degrees of master or doctor of philosophy. This makes the pathologist an ideal collaborator

in research problems, the primary scope of which lies outside the field of pathology.

A number of research problems, the basis of which lies primarily in disciplines other than pathology, still require pathology for their interpretation and solution. Too often, the pathological material in such experiments is discarded without examination. Not long ago, I read the report of a long-term toxicological experiment involving more than 500 rats. The statement was made that the rats were necropsied and no tumors were found in either the control or the experimental animals. It would be virtually impossible not to find many tumors in 500 rats, 20 or more months of age, of any special strain or breed or randomly selected market rats. Of course, a tumor does not exist for the investigator who does not have the training to detect a tumor at necropsy. It is important, therefore, for pathologists to collaborate with experimentalists trained in other disciplines so that the pathological lesions are properly recognized and recorded.

WHAT are the characteristics of a research man? No prevailing characteristic to my knowledge marks a potential investigator, unless it be the possession of an innate drive to explore a new idea even against advice. Certainly, there is no average investigator. Research has been defined in part as finding things without being told. The investigator is able to correlate seemingly unrelated facts. He knows what constitutes proof. Young or old, he must be keen enough to observe his results no matter in what direction his experiment leads and to turn his mistakes to good purpose. The research worker himself is a worthy subject for research, and some day some enterprising student of psychology may determine and record the recipe of his composition.

The greatest caution should be exercised to avoid the discouragement of a young resident who proposes an experiment. The experiment may appear inconsequential and often wholly impractical, but I have found that it is unwise to ridicule any plan for an experiment. It happens ever so often that one of these seemingly inconsequential or impractical experiments leads to results of great importance. It was the usefulness of seemingly useless research knowledge that led Marconi to develop wireless telegraphy. The most important factors in research are a desire to do an experiment and the impatience to get to work on it. All else is subordinate. A proposed experiment is often condemned because it has been performed previously. One needs only recall that prior to the development of insulin therapy for diabetes by Banting and his associates, other investigators had studied the effects of ligation of the ducts of the pancreas. Yet it was Banting who finally extracted the active factor from the islets of Langerhans by using modifications no one had carried out successfully before. It is clear that even though an experiment may have been performed previously something new may be found upon repeating it.

The beginner in research is apprehensive lest he err in his first experiment. Inertia retards many aspiring scientists from taking their first steps in the field of research. One has to get on with the work and realize that mistakes are inevitable. They can, however, often be turned to profit and may lead to the solution not necessarily of the problem under investigation, but rather of another entirely different and often more important one. It does not matter much whether the resident discovers anything new or publishable. The experience gained will be sufficient reward. Those who direct programs of residency training have a responsibility to see to it that these fine minds are given the opportunity to bring their ideas and talents to bear on experimental problems. Finally, the young investigator should be warned that for a large part of the time he works in research he will be doing the hardest and most uninteresting kinds of work that may involve cleaning animal cages, washing glassware, and cleaning up after necropsies. He needs encouragement and consolation together with all the help that can be given him to lessen the onerous duties that constitute so much of research.

THE TRAINING of a pathologist in the modern aspects of service work in clinical pathology has reached a peak in the United States that is unsurpassed elsewhere in the world. However, his reading should not be

limited to factual textbook material. He should be encouraged to read some of the original speculations of the great thinkers in pathology and research. How many residents are advised to read Nicholson's provocative essays on the formation of tumors, or Rokitansky on the humoral theory of disease, or Virchow on cellular pathology? or indeed such classics as the autobiography of Sir Ronald Ross? . . . The training of a pathologist in tumor pathology emphasizes accurate diagnosis of the biopsy specimen—almost never speculation as to the possible causes of tumors.

The resident training program should provide (*a*) more time to think and philosophize; (*b*) more instruction in the design and execution of experiments and the interpretation and application of the results; (*c*) recommendations for reading original contributions to research; and (*d*) access to library facilities that are adequate for the needs of a research worker.

HOW does the admissions committee choose or reject a candidate for medicine, and what is the impact of his choice on research in pathology? It is, I am told, the aim of many admissions committees to select applicants on the basis of high grades in college and the possession of certain qualities . . . that somehow or other indicate that the selected individuals will become good practitioners of medicine. So far as I know, no admissions committee deliberately selects students for medical school who possess the qualities needed for research. Consider the influence on the admissions committee of an answer to a question that the candidate for medical school might be asked. The question may be: "Did you go to the football game last Saturday?" Suppose the reply is "I spent the afternoon in the library reading some early editions of Machiavelli's The Prince," or "I spent the afternoon in a cool, quiet saloon scheming to eliminate some stupid premedical courses." Are these the kinds of answers calculated to get oneself admitted to medical school? And yet one must admit these answers reflect both honesty and originality, two excellent qualities for an investigator.

Dr. Stewart's paper will appear in full in the American Journal of Clinical Pathology.

Health Research Facilities Grants

Expansion of the Nation's health research facilities by at least $120 million is under way as a result of grants awarded by the Public Health Service during the first 2 years of its 3-year grant program.

Financed by an appropriation of $30 million authorized for each year, the grants are allotted for construction and improvement of facilities devoted to research in the basic science areas on such diseases as cancer, heart disease, and mental illness. An amount equivalent to the grant, or more, is supplied by the participating institution.

Approval of 43 new grants totaling $3,698,452, in October 1957, completed allocation of the $60 million appropriated for fiscal years 1957 and 1958. Benefited in the latest action were 39 institutions in 22 States, the District of Columbia, and Hawaii.

Under the new program, grants are approved by the Surgeon General on the recommendation of the National Advisory Council on Health Research Facilities. A total of 251 grants have been made since the program's inception in June 1956.