# CLINICAL INVESTIGATION IN DERMATOLOGY*

CLARENCE S. LIVINGOOD, M.D.

It is a great honor for me to address the membership of this society and its guests in my role as President.

All of us have reason to be proud of this society; in a brief span of 16 years it has reached a stature which is comparable to that of older similar organizations in other fields of Medicine and Surgery. The program for this meeting includes 34 papers; 17 institutions are represented; all but one of the senior essayists are dermatologists or basic scientists associated directly with Dermatology departments. In reading the abstracts of these papers, one is impressed by the wide range of basic science disciplines which are represented.

The perusal of the proceedings of this society, as well as a review of the Dermatology journals, makes it obvious that during the last decade the volume of basic science investigative work, directly related to problems of the skin, has increased by leaps and bounds. I have not conducted a survey, but one would be conservative in estimating that the number of Dermatology departments in this country, in which basic investigative work is conducted on a significant scale, has increased many-fold. Without difficulty, I could name at least 15 or 20 men with previous training in one of the basic sciences who have entered the ranks of Dermatology during the past 10 years. The stimulus of their teachers and opportunity to work with basic scientists, have led others to acquire a significant degree of proficiency along these lines during their fellowship and residency training periods. The caliber of this program year after year is an impressive testimonial to the vital past and still growing interest in basic investigation as it relates to our specialty. It exemplifies the great desire of a constantly increasing number of dermatologists to make basic contributions to the etiology and treatment of skin diseases. As long as this trend continues, one can look forward to the future with the anticipation that our understanding and control of skin diseases will continue to become more satisfactory.

The subject for discussion today was selected because I believe that it is the obligation of this Society to foster superior clinical research as well as basic research. Let us define clinical research. The word "research" means "diligent protracted investigation, especially for the purpose of adding to human knowledge; studious inquiry." Clinical is derived from the Latin "clinicus" meaning "bedridden person." Therefore, the literal meaning of clinical research is "a studious inquiry of bedridden people (1)." Dermatologists, in particular, are justified in liberalizing this definition to include ambulatory patients. To this literal definition of clinical research must be added: the concomitant utilization of the laboratory, scientific experimental planning, appropriate use of controls, and proper statistical analysis of data. The important role of good dermatologic

* From the Division of Dermatology, Henry Ford Hospital, Detroit, Michigan.

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clinical research in advancing our knowledge regarding the etiology and treatment of skin diseases, in increasing the stature of our specialty, and in improving the training of specialists in Dermatology (as well as undergraduate students) is self evident.

Too frequently, claims regarding the effectiveness of new and old therapeutic agents are based on clinical experience rather than scientific clinical investigation. In this connection, it seems appropriate to quote the aphorism: "Clinical experience is a statistic done carelessly in the head, and in which facts that do not agree with the preconceived opinion of the experimenter are too easily forgotten, and those which suit his purpose are overemphasized (2)."

All of us will agree that the great number and variety of incompletely tested therapeutic agents which have been proposed in the dermatologic literature are in contrast to the few which were originally tested according to accepted scientific criteria. Preliminary reports in which the promising therapeutic value of a given treatment is advanced on the basis of trial in a small uncontrolled series of cases are interesting. However, the fact is that many of these papers do more harm than good, in that the quoting and requoting of this type of clinical experience may lead to the unequivocal acceptance of a method of treatment which essentially is valueless, and in some cases, harmful. This state of affairs is not limited to Dermatology. For example, Ross (3) in an excellent article on the "Use of Controls in Medical Research" reported the results of his analysis of 100 unselected current articles, describing some procedure or therapy for various internal medical diseases. He concluded that in only 27 per cent of these papers was it demonstrated that adequate controls were used or that the natural course of the disorder was improved by the treatment which was advocated. The articles which he selected were published in five leading carefully edited medical journals: J. A. M. A., The American Journal of Medicine, Annals of Internal Medicine, Archives of Neurology and Psychiatry, and the American Journal of Medical Sciences.

Unfortunately, some of the problems which confront the clinical investigator cannot be solved easily. Indeed, it is probable that most of us will agree that it is more difficult to plan and carry out adequate clinical investigative studies than to conduct basic laboratory studies of problems relating to the skin.

It is obvious that the clinical investigator has great responsibilities. In contrast to the experimental work of a basic scientist, usually his observations have immediate application in the treatment of diseases in man; an even greater responsibility is involved in an adequate estimate of the untoward side effects of a new medicament. Papers dealing with therapeutic studies are apt to be abstracted in numerous medical journals (as well as Time Magazine, and other lay periodicals), and frequently, are quoted in the advertising literature of pharmaceutical houses. Subsequent reports on the same subject by the *original investigator*, or by others, may disprove the alleged therapeutic efficacy of a given drug or procedure, or reveal important side-effects which were not apparent during the initial clinical trials, but unfortunately, this knowledge is not disseminated through the same channels of information.

Let us consider the qualifications of a successful clinical investigator. It has

been said that "the quality of clinical investigation begins and ends with men of high integrity, ability, and inquiry (4)." The clinical scientist must be a properly trained clinician, but clinical training alone will not make the man a researcher. In addition, his training must include tutelage in the use of controls and the planning of experiments. He must learn about the variability of biological measurements and the proper interpretation of observations. He must be self critical and objective in his approach.

It is not necessary for me to emphasize to this group that special knowledge of experimental physiology, microbiology, biochemistry, physics or pathology is a tremendous asset for the clinical investigator. There is the added factor that a period of training in a nonclinical department is helpful in learning the discipline of scientific methods and planning which are not only applicable but absolutely essential in clinical experimental work.

Those of us who have not had extensive training in one or more of the basic science disciplines may work in partnership with the bacteriologist, biochemist, histologist, physiologist and physicist. Personal experience with several such successful team projects which we have been able to establish with basic science departments at the University of Texas School of Medicine* and the Henry Ford Hospital leads me to believe that this approach can be satisfactory and rewarding for both the basic scientist and the clinician. At the same time, it must be emphasized that good clinical research cannot be carried out by merely arranging for a series of tests to be done in a routine clinical laboratory or any of the various other special departments in the hospital.

A successful clinical investigative study must be planned so that the design of the experiment will make certain that the maximum information is obtained with a minimum of effort. The beginner as well as the experienced clinical investigator should not embark on any project without preparing an outline of the factors which may produce a result and the possible answers which experimental approach will yield. One of the many pitfalls to avoid in planning a clinical investigative project is an attempt to evaluate several variables in the same experiment.

The body of knowledge available to medical investigators has increased to such an extent that many problems can be solved only by the collaboration of experts from a variety of fields. In a few institutions with unusual facilities for dermatologic research, at least several fields of special interest may be represented, and it is possible for the entire group to assist each other in planning and carrying out both basic and clinical experimental work. Under other circumstances, it is essential for the clinical investigator to consult specialists in the basic sciences and in the clinical specialties. Recently, in conducting one clinical study (5), we found it rewarding and indeed mandatory to have the advice and/or the active collaboration of an endocrinologist, a chemist, an internist with special interest in water balance, and a dietitian.

* In particular, we are indebted to Dr. Charles Pomerat, Chief of the Tissue Culture Laboratory, and Dr. Frank Engley, Jr., Associate Professor of Bacteriology, University of Texas School of Medicine.

One of the basic prerequisites in clinical research is the utilization of adequate controls. The classic paper on this subject in the dermatologic literature is that of Pillsbury and his collaborators (6); it was presented at a meeting of this Society. The important factors which contribute to the planning and adequate control of clinical investigative projects involving evaluation of methods of treatment are discussed in a most lucid and authoritative manner. Those of you who have not read this paper will find it a rewarding experience to do so.

Dermatologists are indebted to Sulzberger and his group, and to Siemens for their excellent studies on the evaluation of topical medicaments by the so-called paired comparison method. Their work in this field has stimulated others to use this approach in conducting clinical investigation involving the evaluation of local therapy. Under appropriate circumstances, this method of evaluating local treatment yields valid conclusions. However, the paired comparison method is not applicable unless involvement is bilateral and equal in severity and the lesions in the same stage of development. The patient must follow directions implicitly, a circumstance which may or may not materialize.

Another method of controlling local therapy is to alternate the use of the control ointment or lotion vehicle with the medicament which is to be evaluated; the control may be applied for a few days to one week and the results carefully evaluated; following this, the active medicament is substituted for the control preparation without the knowledge of the patient; or the process may be reversed using the active medicament initially, followed by the control. It is necessary that the control preparation and the topical medicament under investigation have the same appearance; such a study is more accurate if the investigator does not identify the control and the active preparation until the results have been tabulated at the end of the experiment.

It is difficult to subject the appraisal of drugs orally and parenterally administered to vigorous control. The fact is that man resists being controlled. Laboratory experiments involving the *in vitro* effect of an antibiotic on bacteria growing in the test tube is reproducible and predictable, because it depends only on the bacteriostatic and bactericidal effect of the agent which is in contact with the bacteria. The therapeutic result when the same antibiotic is used for the local or systemic treatment of an infected skin lesion is not necessarily predictable or reproducible, because the effect of the antibiotic on the bacteria may be modified by numerous other forces acting on the end organ at the same time. Furthermore, the investigator is just as human as the subject; he may unconsciously affect the experimental result because of his natural desire for a successful outcome of the experiment; he may be too enthusiastic, an attribute which may make him a good psychotherapist but not an objective clinical investigator.

Some of the factors which must be considered in planning a controlled clinical study when we wish to evaluate an orally or parenterally administered therapeutic agent include the sex, age, economic status, occupation, severity of the disease, and the presence or absence of complications. For example, one fundamental consideration in conducting a valid controlled therapeutic study of two samples of patients with herpes zoster is the age factor.

The results of therapeutic studies are far more significant if two appropriate samples of patients are selected, one group treated with a placebo and the other treated with the drug under investigation. The appearance of the placebo and the active drug must be identical; the clinical investigator should not identify the active and the inactive preparations until the end of the experiment. However, even the intelligent use of placebos does not settle the questions which are involved in some therapeutic studies. In a most important paper relating to the pharmacology of placebos, Wolf (7) has shown that the effect of drugs must be assessed "not only with reference to their pharmacologic action, but also to the other forces at play and to the circumstances surrounding their administration." He had the opportunity to observe the effects of various drugs as well as placebos on the gastric mucosa of a human subject who had a large gastric fistula. In his extensive study of this patient, the following factors appeared to be of leading importance in influencing the effects of the drugs and placebos which were investigated: "(1) The state of the end organ at the time of administration, *i.e.*, the effects of forces already acting prior to the administration of the agent; (2) The setting in which the agent was administered, including the route of administration, the presence of the experimenter and the effect of suggestion, implicit or expressed; (3) Conditioning circumstances and previously established habits of reaction."

The habit of quantitative and statistical thought is essential in clinical research. As Mainland (8) has emphasized in an excellent paper on this subject, statistical ideas must be considered in the early planning of a project, because statistical methods cannot be applied to data which have been collected in an experiment which was not planned and conducted correctly. The clinical investigator must be familiar with the elementary general principles of statistics as they apply to clinical research. He must understand the requirements of adequate samples of patients, the principle of random sampling, the influence of chance variations, and the meaning of statistical significance.

Training and experience in the use of clinical research methods are essential in developing specialists in Dermatology. In a department dominated by a spirit of inquiry, the beginner in Dermatology learns to appreciate the imperfections and inconsistencies of the established body of knowledge and he develops a dominant ambition to acquire new knowledge. The opportunity for the resident or fellow to do clinical research during his training period has a profound influence in improving the quality of his observations in his daily contact with patients, without which good practice is impossible.

I have in a sketchy manner re-emphasized some of the basic principles as well as the problems which are involved in clinical investigative studies. It is not necessary to apologize for presenting a paper related to clinical research at a meeting of this Society. The final test of knowledge acquired in basic studies in the laboratory and in animal research is its application to the patient. Furthermore, the answer to some of our problems are probably as simple as was the liver treatment of pernicious anemia.

I have not attempted to compare the relative importance of basic and clinical

investigation. The meetings of this group should serve as a forum for the presentation of both basic research and clinical investigation. I think that it is unfortunate that during recent years, the programs of this Society have included comparatively few papers relating to clinical investigation. In discussing this with some of my colleagues, I have the impression that many dermatologists hesitate to submit clinical investigative papers for the program of this Society. I hope that there is a reversal of this trend. The policy of including a representative number of clinical investigative papers on this program would foster a closer collaboration between clinicians and basic science laboratory workers, a circumstance which is not only desirable but essential. Furthermore, under these circumstances, our meetings would attract the interest of more dermatologists.

Clinical investigation has had an important role in the development of our specialty. Clinical dermatologists as a group have the spirit of inquiry. They have used the laboratory when it is applicable to the problem at hand—recall the work which has been done by some of our colleagues in the field of fungus infections. Some of the future advances in our specialty will continue to be made by clinical researchers. This Society should have a part in this, and it could be done by encouraging the presentation of a representative number of papers dealing with clinical investigation at these meetings.

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