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PRESIDENTIAL ADDRESS

AN INQUIRY INTO THE MEANING OF CLINICAL INVESTIGATION

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Having approached emeritus status in the Society and being Editor of its journal for the past four years, it has not been possible to avoid considerable thought about the meaning of Clinical Investigation.

Frankly speaking, this inquiry has not led to sufficient insight for me to circumscribe its perimeters or to identify its characteristics from those of other sciences. The query has, however, raised some thoughts which I would like to share with you, since we are a society for Clinical Investigation and should have such awareness of its meaning as is consistent with its rapid and inevitable change in character.

I naturally went back to the origin of this Society and its constitution. The objects of the Society, as set down in the constitution, were most desirable but yet were not defined sufficiently for my purpose—so I perused the address of the first President, Dr. Meltzer (1).

It appears that in the beginning the founders themselves may not have been too clear as to what Clinical Investigation would turn out to be, but rather desired to encourage American physicians to make any kinds of objective and orderly observation on patients.

The first President seemed most concerned with a gangrenous disease of clinical medicine which manifested itself through a suicidal process by which each time a scientific growth developed in the field, it was extruded, like a foreign body, to become a special science—leaving clinical medicine to maintain a certain peace of mind, freed from the fetters of maturation into a science. It was by such a process, according to Dr. Meltzer, that the medical sciences, such as anatomy, physiology, biochemistry, etc., broke away.

One stated purpose of the founders was to bring back to clinical medicine those scientific disciplines which it had previously cast out so that one might say that Clinical Investigation represented an endogamous type of marriage between the allied sciences and the art of medicine, for as Dr. Meltzer stated in 1908: "I am of the opinion that clinical medicine as it exists now is made up of two constituents. One part has all the elements of a pure science and ought to be coordinate to the other pure sciences of medicine, and the other part is the real practice of medicine, an applied science which has many elements of an art." It appears that he was partial to the scientific mate of the union for he warned the members, "The constitution does not keep you down exclusively to science but let me tell you; beware of practice. It is a bewitching graveyard in which many a brain has been

buried alive, with no other compensation than a gilded tombstone."

I think it can be said that Clinical Investigation has developed far along the pathways envisioned by the founders of this Society. In fact from some quarters one hears that the content of our program and that of our Journal is investigation all right, but bears only a slight resemblance to anything clinical. Perhaps it may be that Clinical Investigation has become somewhat Frankensteinian to some adherents of practice and perhaps also to some adherents of the "pure" sciences of medicine in the light of the competition which Clinical Investigation offers to the latter. For it now brings to bear in its study of man not only the disciplines of the biological sciences but those of the natural sciences as well and is beginning to encompass the social sciences.

It is of interest that the constitution requires that Society members have the M.D. degree and this requirement may have some symbolic connotation in defining, in a narrow sense, the peculiar differentiation of clinical from other forms of investigation, namely, the investigation of man as opposed to other forms of matter. Man, in health and disease and all things that affect his health, would seem to be the perimeter of the field. In order to study man, the clinical investigator must have both the training and the legal prerogative to do so in a responsible manner.

By and large Clinical Investigation has tended to apply all forms of investigative techniques and disciplines derived from other sciences to the study of man. It has been slow in developing that part which sets it aside from other fields of investigation, namely, the differentiating characteristics of man himself.

As a matter of fact, man is anathema to a very widespread principle of science, namely, the need to control in order to study. Man has been resisting control and seeking freedom throughout the ages, so that it is no wonder that he—and this includes the observer and the observed—has resisted the application of accepted scientific approaches. This factor has been ignored by many clinical investigators and deliberately bypassed by many others through the use of orderly experimental designs and statistical approaches, and through the correct use of the placebo—methods which can, and sometimes do, get the answer in spite of the fact that man is man.

The ability to investigate the more intricate workings of man requires some recognition of the facts that man resists being controlled, that he perceives through other

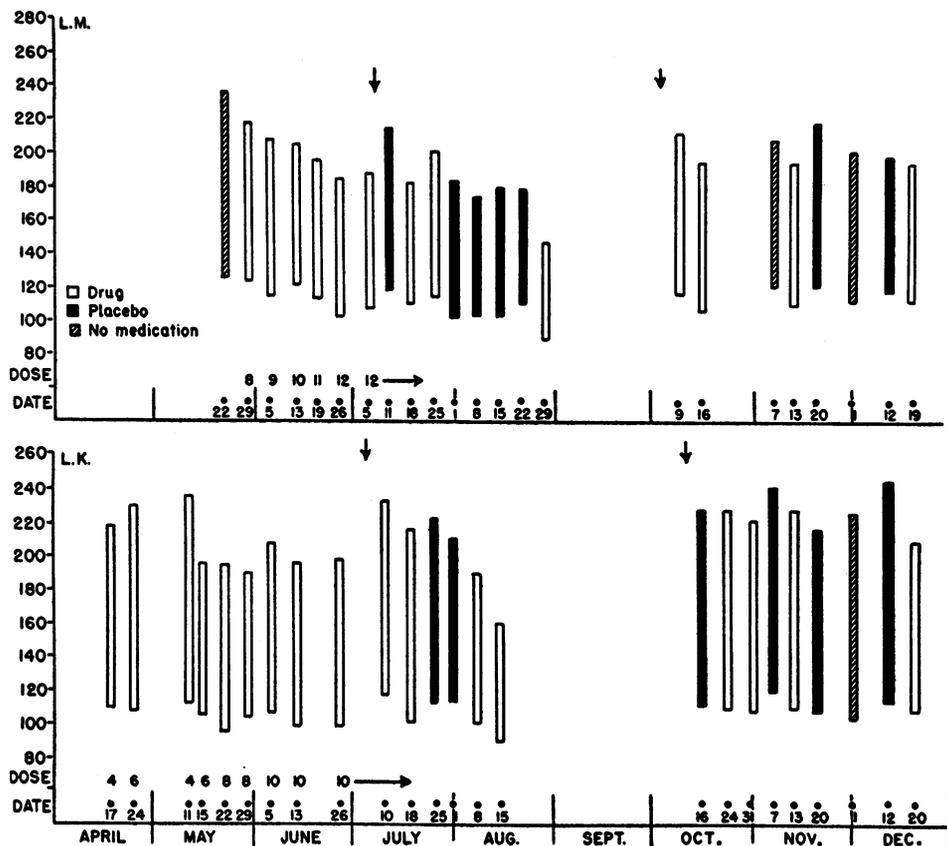


FIG. 1. THE EFFECT OF A DEPRESSOR DRUG ON THE STABILIZED RESTING BLOOD PRESSURE OF TWO PATIENTS HAVING ESSENTIAL HYPERTENSION

The dosage was built up to the indicated maximum and continued as drugs or placebo throughout the period of observation. Abscissa: BP in mm Hg; Ordinate: Dates as indicated. Bars represent systolic and diastolic limits of arterial pressure obtained by the auscultatory method.

than the five senses, that he communicates through the spoken and unspoken word, and that the investigator is just as human as the subject.

Thus we set up such conditions as the "basal state," "bed rest," etc., and may forget that people like bed rest or other forms of control to varying degrees. Some can relax without breakfast and others get angry at being denied it, so that controls may be more or less stressful depending on one's attitude toward them. It is known of course that feeling states, such as anxiety, can profoundly affect physiological homeostasis and that the placebo may be recognized by non-verbal communication.

The clinical investigator himself, through a need to control or dominate the patient, through his reaction to control or discipline of himself, and through his reaction to the success or failure of the patient to respond, may likewise affect the experimental result quite independent of his overt motives and desires or conscious integrity.

The following data from a group of studies to be subsequently reported serve as an example of the challenge to and special identity of Clinical Investigation as exemplified by the interaction of man, the investigator, with man,

the investigated, and the intricacies which result therefrom.

Here are two women (Figure 1) in whom the depressor effects of a drug are being evaluated by one investigator-physician. As the dosage is raised to the point of optimum tolerance one notes a fall in blood pressure which is consistent with the hypothesis that it relates to the drug. It could also be related to the enthusiasm of the investigator and we know that, in this instance, there was such a feeling, so that it seemed appropriate to test the hypothesis further by the random substitution of blank pills for the drug. This procedure was acceptable to the investigator but it was more difficult for him to accept the further control that he, like the patient, should not know which was placebo and which was drug. In relation to the initiation of this control (July 9th), one notes an initial rise in blood pressure in the one case during blank administration and in the other case during the drug therapy, followed by a reduction in BP in both as the investigator accepted the new approach.

At this point, it is probable that as compared to the administration of blanks, the depressor effect of the drug

is evident but certainly not world shaking. It is apparent that further observations of the effect of drug and blank are necessary in order to establish the statistical significance of the rather uninspiring depressor effect of the drug.

During September several phenomena occurred in the investigator which had in common a lessening of enthusiasm in the experiment but which were not known to the patients: (1) there was a lessened enthusiasm for the therapeutic efficacy of the drug and a resistance to continuing the experiment, (2) the investigator volunteered in the armed services for future assignment, and (3) he married and took a two weeks' vacation.

The experiment was then continued as planned, and it is quite evident that the blood pressure thereafter returned to approximate pre-treatment levels in which the drug itself still exerted perhaps a slight depressor effect. It seems quite possible that the patients may have sensed and responded to a change in the experimental atmosphere despite continued administration of pills.

This phenomenon of the interaction of the observer and the observed and the variable response of both to rigidly conceived methods of control, represents one phase of investigation which, if not peculiar to, is certainly a delineating characteristic of Clinical Investigation.

Any dynamic system is altered to some extent by the impact of a direct measurement, but man, particularly, responds also to observational techniques in which neither

physical contact nor direct transfer of energy occurs. This latter response is inherent in Clinical Investigation. Though it cannot be avoided, other responses can be isolated from it by a sophisticated experimental design which recognizes that such an interaction is continuous between the observer and the observed, and that to the subject the Clinical Investigator is always cast in the mold of a physician.

As the intricacies of our techniques require more attention to fewer subjects, this interaction may become a dominant factor in the response. It thus becomes imperative that controls be applied in the positive sense of observing the truth rather than the negative sense of domination.

Clinical Investigation, as elusive as it is, has, I suspect, surpassed the fondest expectation of the founders when they started this Society 44 years ago. When it systematizes man's total behavior and weaves it into the galaxy of other scientific disciplines which it has applied so successfully to the study of man, there may be little to distinguish the art from the science of medicine.

REFERENCE

1. Austin, J. H., A brief sketch of the history of the American Society for Clinical Investigation. *J. Clin. Invest.*, 1949, **28**, 401.