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Conference on Therapy

How to Evaluate a New Drug

THESE are stenographic reports, which have been edited, of conferences by the members of the Department of Pharmacology and Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. HARRY GOLD: The problem of clinical evaluation of new drugs at the present time presents a serious bottleneck to therapeutic progress. The laboratories are bursting at the seams with new chemical agents relating to almost every field of treatment. There are the large numbers of local anesthetics, general anesthetics, adrenergic and cholinergic compounds, the peripheral blocking agents, central nervous stimulants and depressants, cardiac agents, diuretics and others. The pharmacologic laboratories are doing a very good job in screening these materials but there is always the need of getting the final answer from clinical pharmacology, studies made directly in human subjects. Here is where the advance slows down markedly.

Three needs are in evidence here, physicians familiar with the management and sufficiently trained in scientific investigative procedures; sufficient clinical facilities suitably organized for this purpose; and the development of good methods for testing drugs, comparing one agent with another in such a way as to secure the most information with the fewest number of patients in the shortest possible time. These are the problems but in this conference we are going to explore only one of them, namely, methods for clinical evaluation of a drug, how to do this in human subjects in such a way as to obtain a verdict not likely to be reversed. If we are not going to do a particular study ourselves, the results of this conference should help us to see what we have to look for in the reports of others, for one can get a very good notion about the validity of conclusions from the kind of methods that were employed. Dr. William Grace will lead off the discussion.

DR. WILLIAM J. GRACE: It is well known that the response to a particular pharmacologic agent in a group of patients is not invariably the

same or even predictable. When we learn that a certain agent proved effective in, say 35 per cent of the patients, we accept the result and let it go at that. This is one way of evaluating a therapeutic agent. There are other questions which need to be raised and answered and I will confine my comments to some of the experiments that we have recently made in this connection. I refer to the matter of determining the factors in any particular individual which alter the responses to the drug in question from time to time. It helps to understand why an agent may fail to work at one time or produce more effect than anticipated at another.

We have had opportunity to make a variety of observations on the responses of the gastrointestinal tract during various mood and feeling states in our subject, Tom, a man with a gastric fistula. In one instance, he was lying on the table and carrying on a free discussion of appetizing foods which appealed to him. This was late in the morning, he felt hungry, and expressed the desire to eat. At this time the stomach showed an increase in blood flow, total acid secretion and gastric motility. Under these circumstances the introduction of beef bouillon into the stomach was followed by further increase in blood flow and secretory and motor activity. The result was different when the same experiment was made at a time when the subject felt discouraged and depressed, preoccupied with self-criticism because of his inability to effectuate a deal in the purchase of a house. During this period he complained of fullness after eating, lack of appetite and loss of interest in eating. At this time the same beef bouillon stimulus was followed by little or no change in the secretion or motor activity of the stomach.

Changes in stomach function during anger were observed in this subject. Tom was discussing his attitude toward a man who had recently

discharged him from his employment under circumstances which the subject felt were embarrassing and humiliating. He showed visible anger. In this state the stomach showed an increase in blood flow, hydrochloric acid and motility.

During fear the opposite was noted. Tom was suddenly faced with the fact that his supervisor would soon become aware of Tom's lack of attention to carrying out the jobs that he had been assigned. The professor entered the laboratory and searched for a protocol book which Tom was thought to have filed. Tom became frightened that his laxity would be discovered and he would be discharged. However, the professor found the book and walked out satisfied. Sharp changes in the behavior of the stomach took place. During the sudden experience of great fear there was blanching of the mucosa, decline of secretion and cessation of motor activity. During the period of recovery of confidence the blood flow increased and motor activity rapidly returned. Such changes in either direction occur rapidly without the individual necessarily verbalizing any feeling state that may be associated with them. In the laboratory, changes often appeared in the stomach before the particular drug was introduced. The nature of the change depended on his attitude at the time. For example, when Tom was frightened by the prospect of taking a large and disagreeable looking pill, his stomach became pale and hypoactive before the medicament was administered. On another occasion Tom became angry at being given an injection. Hyperfunction of the stomach was noted before the injection.

When the subject ate an average meal at a time when he felt hungry and was interested in eating, the gastrocolic reflex was brisk, resulting in increased blood flow, motor activity and secretory activity in the large bowel. It was not brisk, however, when the food was introduced directly into the patient's stomach or when he forced himself to eat without much appetite. Under these circumstances none of the changes indicating activity of the gastrocolic reflex took place.

An attempt has been made to get around the difficulty of persons reacting differently to different laboratory situations by making use of a standard type of stress stimulus. This has not proved very successful, since different persons exposed to the same trying circumstances react in different ways to it. In one group of experi-

ments, observations on the large bowel were made while the subjects were exposed to the stressful situation of having a tight metal band clamped around their head. In one subject the bowel became very pale and hypomotile during the period of the intense pain; this man later reported that he had been overcome with feelings of intense fear and fright. In another subject the same situation caused an increase in the blood flow and an increase in the motor activity of the large bowel, this person reporting that he was not frightened by it at all but was in a state of conflict over his wish to go ahead with the experiment and angry feelings at us for subjecting him to such an uncomfortable procedure.

The effect of a drug differs with the patient's mood at the time it is given. When our subject Tom was angry, the stomach showing high color, high acid secretion and hyperfunction, a dose of 0.6 mg. atropine failed to alter the motility or secretion. On another occasion when he was feeling more calm and secure and cheerful in his attitude toward us, the same dose of atropine was followed by cessation of motor activity in the stomach. Similarly in the colon, on a day when afistulous, he was clearly preoccupied with thoughts that he was being treated as a freak, was embarrassed and humiliated by the procedures and wished he had never gotten involved in them, an injection of 2 mg. of atropine intravenously was followed by no significant change in blood flow, secretory or motor activity of the bowel. At a later date during a time when he was feeling very much more cheerful and kindly disposed toward the experiment and laboratory procedures, the same dose of atropine resulted in marked hypofunction of the colon.

What I have pointed out here applies not only to atropine but also to the effect of food and other drugs such as physostigmine, prostigmine, acetylcholine and histamine. These experiments all go to show that in evaluating a drug one needs to know not only the nature of the drug and the dose but also the status of the individual at the time the drug is given.

DR. GOLD: These very interesting experiments cited by Dr. Grace have to do with the reaction of the total person, the influence of mood or attitude on the response to a drug. His examples are drawn from observations on the gastrointestinal tract but the same can be shown to apply to responses of the blood pressure, the heart, or any other functional system in the body.

Dr. Grace points out that we fall short of understanding the effect of a drug unless we observe it in action during different emotional states and he suggests that in the evaluation of a drug we should first ascertain and define the patient's mood or attitude. Perhaps we can have some discussion of another approach to the evaluation of a drug, one that does not necessarily require such definition of the patient's emotional state. I have reference to a comparison of one compound with another, an attempt to determine, for example, by how much one compound is more potent than another in relation to a particular effect. The moods and attitudes of the patients used in such comparisons are very important and influence the results but it is possible so to design the evaluation that whatever influence the emotional state of the patients may exert is canceled out by having it distributed equally between the two compounds used in the comparison. The two compounds may involve an allegedly potent agent and a blank of such physical properties as to render a distinction between the two impossible except through some pharmacologic potency which may exist. On the other hand, the two compounds may both be potent and we test them to determine a difference in potency. In this type of evaluation of a new drug there are two indispensable elements: one is the notion of a comparison of one thing with another, the other is the factor of the double-blind procedure which calls for such an arrangement of the investigation that neither the patient nor the doctor is aware of the identity of the two agents until the results are in and analyzed. This is imperative to avoid the influence of subconscious bias. The failure to use the double-blind test and the placebo in the attempt to evaluate a new drug is responsible for a large proportion of erroneous conclusions in clinical testings. It is particularly noteworthy in drugs used for the treatment of gastrointestinal symptoms, hypertension and angina pectoris. I am not sure why it is that the use of a placebo is considered by many physicians objectionable in a method of clinical evaluation and why there seems to be so much resistance to the idea that the experimenting doctor and the patient should remain in the dark about the identity of the agent until the comparison is finished.

DR. FRANK C. FERGUSON, JR.: Dr. Grace has cited examples showing how the patient's moods can influence the effects of a drug. Could we hear

something about the influence of the doctor's attitude on the effects of a drug?

DR. GOLD: It is not difficult to find examples of the profound influence of the doctor's attitude. The case of khellin is a good illustration of recent vintage. This material was introduced a few years ago for the treatment of cardiac pain in coronary disease and for bronchial asthma on the basis of laboratory experimentation showing that it exerts a potent smooth muscle relaxing action. Clinical trials proved that by far the larger proportion of patients with angina pectoris obtained partial or complete relief with this drug. A placebo was used in some of these studies but the physician knew which was which at the time of his questioning the patients. A group of us undertook the investigation of khellin by the double-blind test, using a placebo which in physical appearance was indistinguishable from the tablets of khellin, and arranged observations in such a way that neither the patient nor the doctor was aware of the identity of the two materials until the results were all in and analyzed. After some 3,000 answers regarding the effect on pain of the placebo and khellin given to the same group of patients, the results showed that if the patient and the doctor were kept in the dark regarding the identity of the agents, the placebo and khellin could not be distinguished with respect to the effect on cardiac pain.

The whole history of therapeutics, especially that having to do with the action of drugs on subjective symptoms, demonstrates that the verdict of one study is frequently reversed by another unless one takes measures to rule out the psychic effect of a medication on the patient and the unconscious bias of the doctor. The double-blind test insures this.

DR. FERGUSON: You speak of the need for the double-blind test in cases where drugs are tested for their effects on subjective symptoms. How about so-called objective matters? Do you believe that the double-blind test is necessary there to avoid error in interpretation?

DR. GOLD: I think it is well that you used the term "so-called" objective. I am beginning to wonder whether there are any truly objective observations. In the study of drugs in hypertension, a measurement of the blood pressure would certainly seem to be an objective criterion but I have a notion that the reading of the blood pressure also depends on how the doctor feels about the agent. Subconscious bias is a very

subtle mechanism. Results of a study gain considerably in validity if the doctor making the observation, subjective or objective in nature, does not know whether it is the placebo or the medication in question he is concerned about.

DR. BENJAMIN JABLONS: How important would a placebo be in evaluating the potency of a diuretic agent?

DR. GOLD: In that case, of course, the particular agent is compared with a standard. What would you think, Dr. Cattell, about the need for a double-blind test in a comparison involving a diuretic effect as a measure?

DR. MCKEEN CATTELL: It should be done as a double-blind test. There is always the possibility of a subjective element coming into the experiment at one point or another and influencing the results.

DR. PAUL REZNIKOFF: One of the least subjective measurements is that of the iron content of the blood in an anemic patient when following the improvement in the hemoglobin value during medication. Attempts are made to diminish dependence on subjective impressions and verify results with hemoglobin values and hematocrit readings. In these patients attempts have been made to determine the relative value of various iron compounds and on the basis of such objective measurements it has been stated that some forms of iron are more effective than others. However, if one views the objectives in these cases in more common sense terms, it is extremely difficult to find any substantial difference in the efficiency of iron compounds. I wish to suggest that when one is dealing with human beings, it is very difficult to have a purely objective measurement.

DR. GOLD: You mean that in all so-called objective studies or studies using objective measurements, subjectivity seems to creep in somehow.

DR. REZNIKOFF: Yes, honest subjectivity. I do not refer to those cases in which a person wishes to prove something.

DR. GOLD: I am glad to hear you say "honest subjectivity." I think it is a matter of the greatest importance to recognize that the bias on the part of doctors that is most serious is the unconscious bias, the kind of thing of which the doctor, himself, is not aware.

I think Dr. Reznikoff has pointed up an important factor in the comparison of therapeutic agents, namely, the selection of appropriate criteria for judging total results. A comparison

of iron preparations in the treatment of anemia by the measurement of red cells, hemoglobin and hematocrit may possibly show differences between one compound and another, which fail to emerge when a comparison is made in terms of the well-being of the patient as a whole.

DR. CATTELL: Dr. Grace's results are certainly significant in showing the importance of different mood states in relation to the action of a drug. In this connection, however, there is another point which seems to me of great value to the physician, and that is the fact that he would like to know what the reaction to a particular agent is likely to be in the general population. The doctor has to start somewhere. Studies of a drug should provide him with some notion as to the probability of the drug proving useful in a particular situation. If we use a suitable control agent, we can determine whether the particular drug is better than another or has the same effect as another on the average population.

DR. GOLD: What Dr. Cattell has just said touches on an important aspect of the comparison of drugs in humans, namely, the matter of selection of suitable patients for investigation. If it is something about the general population that one is looking for, then the study patients must be truly representative. The same applies if the problem relates to some specific class of patients.

DR. ROBERT D. HUEBNER: How are you going to do the double-blind test in a situation such as anticoagulant therapy in which the doctor has to prescribe or order a day-to-day dose on the basis of the prothrombin test? He has to know the result of this objective test before he can prescribe.

DR. GOLD: You are quite right if what you are thinking about is a doctor treating a patient. When he does that he has in effect already assumed that dicumarol is valuable and he proceeds to use it. That, however, is not what we are discussing. We are talking about investigating a drug, let us say in this case dicumarol. Now we are in the position of trying to determine whether it is valuable. In such a situation the double-blind test is imperative and the difficulty you mention is easily overcome by having one person carry through the dicumarol treatment while another person to whom the nature of the treatment remains unknown, whether placebo or dicumarol, makes the decisions concerning the clinical course and complications.

DR. HUEBNER: But if the patient begins to bleed, the doctor and the laboratory person will have to get together to find out whether or not it is due to the dicumarol.

DR. GOLD: Yes, that is correct. This would interrupt the experiment. One might add that if the person in charge of the dicumarol dosage and prothrombin testing keeps a close watch on the situation, the effects should rarely if ever get out of hand and bleeding due to dicumarol should rarely occur.

DR. WALTER MODELL: Dr. Gold, one of the problems that presents itself during the investigation of a drug arises from the fact that the patient himself may know that he is the subject of an investigation. This information is highly charged and may have a bearing on the results. Perhaps you might wish to elaborate on this point.

DR. GOLD: It is a very important point. The impact of the patient's knowledge that the medication is part of an investigation is properly distributed only when all patients are treated. Do not have a treated and an untreated patient in the study. Treat them all with a tablet, or a solution, or an injection, as the case may be, one with the allegedly potent agent and the other with something that looks, tastes and smells exactly like the first but is a dud. All the patients in the study should appear to be exposed to the same things.

DR. HORACE S. BALDWIN: I believe this point has already been made, but I should like to refer to our own experience in allergy which leaves us with little doubt that a placebo may cause considerable improvement in the patient's symptoms. We had an opportunity to compare a vaccine for hayfever with a placebo. We did not do the double-blind test because the doctor knew which the patient was receiving. The results were unequivocal in showing the value of a placebo in a "subjective" illness.

DR. GOLD: The significance of your point about patients showing improvement in symptoms as the result of a placebo cannot be over-emphasized. It can be demonstrated in about 30 or 40 per cent of all patients with all sorts of disorders. This fact is responsible for the vast literature on drugs that have come into therapeutics with high promise and have left the scene with little loss.

DR. SOLOMON GARB: Is a placebo necessary in relation to mortality rates for treated and untreated cases?

DR. WILLIAM T. FOLEY: I would like to make a point here in regard to mortality statistics as related to our study on dicumarol in coronary thrombosis. We placed most dependence on the course of mortality rates. The design of the study called for the alternate case method of treated and untreated cases in the sixteen hospitals. We were a bit troubled, however, by the fact that in some instances this plan for the selection of cases was disturbed. Here was a new drug supposed to be helpful for a disease which carried a high mortality. The word soon got around among the patients in the hospitals and among the families that certain patients were receiving the drug and others were not. In many instances great pressure was brought to bear to see that certain cases would receive it. It raised some question in our minds as to how far one might properly go in judging the value of a method of therapy by the mortality statistics.

DR. GOLD: This is just one more illustration of the importance of seeing to it that there are no untreated cases in a study of a new drug or treatment.

DR. REZNIKOFF: We have in the audience an authority on this study, one of our alumni, Dr. Quick. I wonder if we could have some of his impressions.

DR. ARMAND J. QUICK: I agree fully with the stress which has been placed here on the double-blind test. Specifically, in the matter of anti-coagulant treatment of heart disease I think that a valid evaluation requires that one person governs the dicumarol, that another looks after the patient and that a third evaluates the treatment. No matter how honest we try to be, if we become enthusiastic we are carried away, and in some manner or other transmit the enthusiasm to the patient. I have made the remark on other occasions that the more impressive the clinician, the more engaging his personality, the worse he is from the standpoint of evaluating drugs, because his personality very often dominates the patient.

DR. GOLD: I suppose that what you are suggesting is that we should not try to alter the personality of the investigator but let him enjoy whatever personality he has and neutralize the bias it might create by balancing the effects of the drug against the placebo.

DR. QUICK: That is the point.

DR. GOLD: I wonder if we might have some comments on this subject from Dr. Bross who is an expert in vital statistics and has had much to

do with designs for the investigation of therapeutic problems.

DR. IRWIN D. J. BROSS: I am very much impressed with the remarks I heard today. It seems as though this group has a level of sophistication that I have not often encountered in my work with medical groups. I might say a word about this third person who was mentioned by Dr. Quick. I guess this is more in the nature of a statistician's type of third person. He can be replaced by a machine. The reason I mention this is that frequently it is inconvenient to have the decisions made by a third person. There are many situations in which decisions can be made by a pair of dice which represent a third person in this particular sense. If a pair of dice sounds unscientific, you can call it randomization, and you can use a random number table which is perhaps not as illegal looking as a pair of dice.

DR. FERGUSON: Since the matter of statistics has been brought up, I should like to remark that I have an intense prejudice against the mass of statistics that accompanies the introduction of new drugs. It seems to me that statistics as they are so often used are too often misleading. Many people believe that they eliminate chance when in fact they merely give an idea as to the probability of the results being due to chance. There is also the fact, which is often overlooked, that statistical analysis of the results does not correct the defect of a bad experiment.

DR. BROSS: Yes, but I want to point out where statistics do come in. Actually, there are two things which interfere with the evaluation of drugs. The first is what might be termed the experimental error, sampling variation. This is essentially the factor that is supposed to be controlled by statistics. The second thing is the particular factor that has received special attention at this conference, namely, bias. The standard statistical tests do not in themselves control bias. Analysis by statistical technics is based on the assumption that the results are unbiased. I would agree, therefore, that there is a great deal of statistical, or presumably statistical, material that is published which is completely misleading simply because of the belief that all

that is necessary to solve a problem is to put down a little statistical arithmetic. Much more than that is necessary. The problem is much more complicated.

DR. GOLD: I presume that the item to which you refer is the design as to bias before the experiment is actually carried out.

DR. BROSS: Yes, the design as to bias.

SUMMARY

DR. GOLD: This conference directed its attention to the problem of the clinical evaluation of new medicinal agents as one of the major issues in therapeutic progress: How to secure verdicts in the comparison of one drug with another which stand a reasonable chance of escaping reversal. In an account of interesting experiments on the gastrointestinal tract it was pointed out that the effect of a drug varies greatly with the patient's mood and that the effect may be significantly altered with a change in the mood. The discussion indicated how such factors might change results in the evaluation of a therapeutic agent. Special attention was directed to the use of the placebo, the double-blind test, statistical analysis of the data and experimental design to eliminate bias. Emphasis was placed upon the unconscious aspects of bias of the physician, a subtle mechanism which contrary to his best intentions may give rise to misleading results. It was a noteworthy feature of the various discussions that the control of this factor by the double-blind test is now recognized as imperative for the valid evaluation of medicinal agents, not only with respect to the study of subjective symptoms such as cardiac pain but also in studies involving so-called objective measurements such as iron in anemia, diuretic agents and anti-coagulants in thrombotic diseases. The conventional design of the treated and untreated groups in a clinical evaluation of a medicinal agent is giving way to the plan which calls for treating all patients, where possible, with the agent in question or with a placebo, the two being indistinguishable in physical form or appearance and their identity unknown to patient or investigator during the experiment.

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