

lowered incidence is due, in my opinion, not to increased knowledge of nutritional needs among those who drink alcohol but to improved economic circumstances, which permit them to buy not only more alcohol but also more food. Diseases due to insufficient amounts of protein have been somewhat neglected because of pronounced interest in vitamins in recent years. Two great unknowns face the physician when he considers nutritional problems. The first is the reason why some patients have deficiency states and others living under apparently similar conditions do not. For example, a man with carcinoma of the esophagus who goes for six months eating almost nothing will lose 40 to 50 pounds (18 to 23 Kg.) and yet not commonly show a specific vitamin deficiency. Often a well nourished patient with some other disease, who is on a deficiency diet for only a short time, will show a definite deficiency state. The second and more important question is: What will happen to the human race when for three or four generations it has been fed adequately? No one has any idea. In the last 50 years the standard rate of growth and weight of experimental animals has changed dramatically. The Oriental who lives in California and eats as Americans do has increased his weight and height so that he is considerably taller and heavier than is his counterpart in the Orient. Just how long this is going to continue, and what will be the eventual normal weight, height and rate of growth of man and woman is not known. There is something to suggest that bigness alone and rapid rate of growth alone are not desirable, because among some experimental animals, for example, resistance to certain diseases at least is not as good among animals that are well fed as it is among those who are not so well fed. Although there appears to be a definite ideal to be accomplished by adequate nutrition, there are other related problems in regard to resistance to disease, and possibly the development of degenerative diseases, which must be carefully considered.

DR. HYMAN I. GOLDSTEIN, Camden, N. J.: Aristotle recommended roast ox liver for the cure of night blindness. Hippocrates, Paul of Aegina and Celsus gave liver therapy and successfully cured night blindness. Goat liver was also used. The Babylonians and the Assyrians also knew of this (vitamin A) deficiency and the value of liver therapy. C. S. Engel of Berlin, Germany, in 1896-1898 used "sanguiform" made from the fetal "blood-making" organs—liver, duodenum, stomach, spleen and bone marrow—and observed the rapid erythropoietic and granulocytic response.

DR. TOM D. SPIES, Birmingham, Ala.: I grew up in an area where many of my playmates and their families had pellagra. The incidence from my boyhood days until 1937 remained high. Since the advent of nicotinic acid therapy the disease in the Southern part of the United States has been eradicated, to all intents and purposes. Imagine, in the past three years working in a clinic where we see some 11,000 patients a year, we have not found a single case of pellagra. This is a fact worthy of recording. Dr. Wirts asked about the incidence of refractory cases of so-called nontropical sprue. I think that would depend on a physician's relation to the members of the profession in the rest of the community. I found in Birmingham that a certain group of physicians was sending me only patients who would not respond to anything, and as long as I dealt only in that group I had 100 per cent of such cases. If they are refractory cases, and if the doctors have given them all available forms of treatment, the physician to whom these patients are referred is going to get an equally poor result. When my associates and I began a different type of search for patients with anemia we found a great many virgin cases, so to speak; still we were not satisfied, and that is one reason why we went to study tropical sprue in Cuba. There we found about 6 per cent of the patients to be more or less the type of which Dr. Wirts spoke. Treatment may result in little benefit but not much. Most lecturers tend to talk about 94 per cent of their cases and to leave out the 6 per cent that are refractory, and I am grateful to Dr. Wirts for making the figures balance properly.

1. Mainland, D.: Statistics in Clinical Research: Some General Principles. *Ann. New York Acad. Sc.* 52: 922 (March 10) 1950.

USE OF CONTROLS IN MEDICAL RESEARCH

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It is not surprising that laymen develop many inadequate methods of treatment for various disorders that beset the human. If an ache or pain disappears after the use of this or that remedy, it is evidence enough, to the scientifically untrained, of the efficacy of the remedy as a cure. That one event precedes another in time is the first logical step in working out a cause and effect relationship. But our untrained friends, and, frequently, trained medical scientists, stop at that stage of reasoning and experimentation. The next step is to realize that time sequence makes possible a causal connection but does not prove it. That proof is what science demands.

On reading current medical journals, one is impressed by the number of articles which extol one or another form of therapy, but which frequently lack proof of scientific merit. The great number and variety of incompletely tested treatments that are proposed as being of value, often for the same disease process, stand in bold contrast to the few which are rigidly tested according to accepted scientific criteria. It is the purpose of this study to analyze a representative group of medical articles according to one essential criterion: the use of adequate controls.

Controls are untreated patients, essential to any scientific experiment because the variable factor being measured must be compared to constants or to known variables. The course of a disease process following a form of therapy must be shown to be improved over the natural course of the disease or over other standard treatment, and in a statistically significant number of cases. This standard seems clearly necessary for an adequate evaluation, but my data indicate that it is often misused or omitted. Thus, there creep into medical literature many treatments which are quoted and requoted and finally unequivocally accepted, but which could not stand rigid scientific scrutiny.

The use of controls is, of course, an essential but preliminary step to the use of a quantitative method in experimentation. From comparison of the treated with an untreated group, the basis for statistical comparison is laid.

Mainland¹ states, "Statistical ideas, to be effective, must enter at the very beginning; i. e., in the planning of an investigation. These ideas however, lacking in so many published reports, are even less frequent in the unpublished efforts of clinicians to assess the value of their treatments. There must be something wrong with so-called scientific medical education when a young physician says that he has obtained promising results by treating [a certain syndrome with a certain agent] and yet cannot understand why a professor of pharmacology should ask about controls."

MATERIAL

The material reviewed in this article consists of 100 current articles from five leading American medical periodicals. These include: THE JOURNAL OF THE

AMERICAN MEDICAL ASSOCIATION, the *American Journal of Medicine*, *Annals of Internal Medicine*, *Archives of Neurology and Psychiatry* and *American Journal of the Medical Sciences*. The articles were published between January and June of 1950 and were the first 100 to deal with some procedure or some form of therapy that was recommended or condemned. The journals were studied at random until 100 such articles were evaluated; there was no artificial selection and no exclusion. Only articles reporting a group of cases were included.

The articles were classified as: those which used adequate controls; those which used inadequate controls only; those which used no controls, and those which by nature precluded controls. A satisfactory control was defined as a number of untreated patients, or procedures, approximately equal to the number treated. These were managed in exactly the same manner as those treated, with the specific form of therapy being tested as the only variable factor. Controls that were held to be inadequate were those in which the number of untreated patients was too small, a different time or place or other variables were utilized in comparing the treated and the controls, or controls were not subjected to the same physical or emotional conditions as those treated (injections and roentgen radiation). Use of controls was held to be impossible when there were reported small numbers of unusual cases in which use of controls obviously could not have been expected or when the severity of the disease was such that none should be left untreated.

The results were as follows:

No control	45 per cent
Inadequate control	18 per cent
Well controlled	27 per cent
Control impossible	10 per cent

It is therefore seen that only 27 per cent of this sample of current recommended therapy can unquestionably be shown to improve the natural course of the disorder. Other therapy may well be beneficial, but verification of its value is not apparent in the accurate and predictable method of science. A bibliography of the articles analyzed is available on request.

ILLUSTRATIVE EXAMPLES

The following are summaries of illustrative articles demonstrating the need for adequate control:

AYMES, E. W., and PERRY, S. M.: Stellate Ganglion Block in the Treatment of Acute Cerebral Thrombosis and Embolism: Report of 44 Cases (*J. A. M. A.* 142:15 [Jan. 7] 1950). The authors took 44 patients with cerebral thrombosis or embolism and treated them by means of cervical sympathetic block. Of the 44, 28 were stated to have shown improvement within 15 to 60 minutes. The criteria for improvement were frequently difficult to measure, and consisted of better speech, increased alertness and "improvement in behavior." No mortality rates were given for comparison with general figures or with data on an untreated group. No figures were presented to show the length of time the patients were followed or the ultimate outcome. Most important, was their improvement greater than it would have been if a stellate block had not been done?

In a disease process so variable in outcome as "stroke," in which patients show all degrees of damage between slight neurological or psychic change, to

sudden death, it is difficult to evaluate any therapy except by careful comparison of groups of treated patients with controls.

The next article was done in a scholarly way from an outstanding institution, and yet without controls, in a disease that is notably variable and unpredictable:

COLLINS, H. S.; WELLS, E. B.; GOCCKE, T. M., and FINLAND, M.: Treatment of Primary Atypical Pneumonia with Aureomycin (*Am. J. Med.* 8:4 [Jan.] 1950). The authors took 40 cases of primary atypical pneumonia and found that "each showed improvement in fever and symptoms," concluding that aureomycin caused such improvement. Their work was well done, and laboratory and roentgenologic studies were accurately correlated with clinical observations, but a similar group of untreated patients was not compared. The authors state: "Definite to marked improvement occurred in every patient within the first day or two after aureomycin was started but in some instances the condition of the patient at that time was such that the improvement may have been coincidental or at least could not with any assurance be ascribed to the action of the antibiotic."

With the simple addition of a control group, such ambiguity would have been obviated. The results would be clear. If the treated patients as compared to a control group had less fever, shorter duration of illness and lower mortality or complication rate, the recommended therapy would impress even the most skeptical.

Both the above articles included data on a sufficient number of cases to be statistically important and were studies on diseases that could easily have been controlled. (In a disease such as typhoid, one would be more reluctant to withhold therapy to a control group.) In contrast to the above, the next article should be considered:

BEST, M. M.; COE, W. S.; MOORE, J. W.; REED, E. S., and CLAY, H. L.: Irradiation of the Pituitary Gland in Hypertensive Vascular Disease (*Am. J. Med. Sc.* 219:276 [March] 1950). These investigators divided 43 hypertensive patients into two groups, into 25 treated and 18 untreated controls. All patients were placed under the x-ray machine and all thought they were actually receiving roentgen radiation; however, actual radiation was not used on the controls. The patients were then followed for symptomatic improvement and blood pressure changes; they were all evaluated in the same circumstances. Symptoms improved in 68 per cent of those actually treated, and in 77 per cent of control patients. There was no significant change in blood pressure, all readings being made under similar conditions.

A previous pituitary radiation study using no controls, which had apparently prompted the above study, had disclosed improvement. We are now able to evaluate this therapy more truly. The above article also dramatically illustrates a commonly overlooked point: the psychic element of treatment. This must always be regulated and made as constant as possible in any disease with large emotional factors.

The following report, which was possibly prompted by unjustified lay press publicity and incompletely controlled medical observations,² deserves study:

HOAGLAND, R. J.; DEITZ, E. N.; MYERS, P. W., and COSAND, H. E.: Antihistaminic Drugs for Colds: Evaluation Based on a Controlled Study (*J. A. M. A.* 143:157 [May 13] 1950). The authors administered various antihistamines to 190 subjects

2. Brewster, J. M.: Antihistaminic Drugs in Therapy of Common Cold. *U. S. Nav. M. Bull.* 49:1 (Jan.-Feb.) 1949.

passed the actions attributable to the drugs. He warns of the difficulty in evaluation of new drugs in patients and urges curbing of enthusiasm until the physiological effects of the placebo are taken into account.

In a recent editorial, "Are Statistics Necessary,"⁶ in THE JOURNAL it was stated: "If he [the investigator] is developing a new therapy, he must know how to set up fourfold tables comparing treated with untreated subjects and must know how to compute the probability that apparently favorable results were accidental."

Workers in other fields now recognize the necessity for controls. The sociologist Greenwood states,⁷ "Control, we may recall, involves establishing a reliable contrast between two situations so that only the one factor under scrutiny remains free and is allowed to vary. Effective control is the key to the entire experimental procedure. It is essential for the accuracy of conclusions. Without proper control we cannot be certain that the causal nexus which we seek to establish is a real one. When an experiment has been conducted without good controls, we cannot know whether an observed effect is actually attributable to the hypothetical cause or to some other equally uncontrolled factor. We cannot tell whether the result would have been the same in the absence of any one of the factors."

It should be emphasized that the use of controls is not just a tool of highly specialized teachers or research men working with tremendous volumes of material. It is equally important to the ordinary practitioner of medicine who treats much smaller numbers of cases. Such men are at the "grass roots" of medical practice and theory and must learn to evaluate various treatments and procedures.

Although the use of comparable controls is an ideal, there are numerous instances in medicine in which small groups of unusual cases, or isolated observations, occur and will merit reporting. Observations of this type obviously cannot be as carefully controlled but frequently have definite merit. The standard outlined above must, of course, be modified or omitted in such circumstances.

SUMMARY

1. One hundred consecutive and unselected current medical journal articles describing some procedure or therapy for disease were analyzed from the standpoint of the use of controls.

2. It was found that in 45 per cent of these articles the investigators made no attempt to compare results of the specific therapy described to those in an untreated control group; 18 per cent used a control that was considered inadequate.

3. Specific examples illustrating both the presence and absence of adequate controls are cited.

4. A general discussion of the problem is presented.

5. It is suggested that a skeptical attitude be maintained toward all therapy or procedures proposed as effective unless adequate untreated parallel cases are compared. This ideal attitude must, of course, be modified when conditions prevent its adoption.

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NEOMYCIN: RESULTS OF CLINICAL USE IN TEN CASES

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Neomycin, one of the newer antibiotic agents, is produced by a species of *Streptomyces fradiae* present in the soil. It was discovered by Waksman and Lechevalier¹ in their search for an antibiotic agent that would be effective against streptomycin-resistant strains of *Mycobacterium tuberculosis*. Neomycin is a basic compound readily soluble in water and most active in an alkaline medium. It is relatively thermostable and is active against numerous gram-positive and gram-negative organisms. It is active also against streptomycin-resistant organisms; it has considerable in vitro activity against different forms of *Myco. tuberculosis*, in some instances showing greater activity than streptomycin. Since there is considerable tendency on the part of tubercle bacilli to develop resistance to streptomycin, the therapeutic possibilities of neomycin against clinical tuberculosis are being pursued. Waksman and his associates² also found that neomycin had only limited toxicity in laboratory animals and was highly effective in vivo against a variety of pathogenic organisms.

It was with the good prospect that this product would reduce further the spectrum of pathogenic bacteria unaffected by existing remedies that the present study was undertaken. Organisms naturally resistant to the antibiotic agents at hand and those which acquire a resistance during therapy and maintain this state in the present and subsequent hosts are the most important stimuli in the search for new and effective antibiotic agents.

Waksman and Lechevalier¹ emphasized that before a new antimicrobial agent can be considered to have chemotherapeutic potentialities it must be less favorable to the development of resistance among organisms and less toxic and more potent, alone or in combination with other agents, against pathogenic bacteria than

6. Are Statistics Necessary? editorial, J. A. M. A. 143:1260 (Aug. 5) 1950.

7. Greenwood, E.: *Experimental Sociology: A Study in Method*, New York, King's Crown Press, 1945.

The neomycin employed in this study was secured from Dr. G. L. Hobby, Charles Pfizer & Co., Inc., Brooklyn, Dr. L. W. Smith, the Commercial Solvents Corp., Terre Haute, Ind., and Dr. A. Gibson, Merck & Co., Inc., Rahway, N. J.

Dr. Selman A. Waksman aided this work by his counsel. The staff of the Urologic Department of the Pennsylvania Hospital, especially Drs. Leon Herman and Lloyd B. Greene, participated actively in this work, and Miss Eileen Randall gave technical assistance.

Director, Medical Divisions of the Pennsylvania Hospital and the Benjamin Franklin Clinic (Dr. Duncan), bacteriologist, Pennsylvania Hospital (Dr. Clancy); Rutgers University research associate at the Pennsylvania Hospital (Dr. Wolgamot), and assistant physician to outpatients, Pennsylvania Hospital (Dr. Beidleman).

1. Waksman, S. A., and Lechevalier, H. A.: Neomycin: A New Antibiotic Active Against Streptomycin Resistant Bacteria, Including Tuberculosis Organisms, *Science* 108:305-307 (March 25) 1949.

2. Waksman, S. A.; Hutchison, D., and Katz, E.: Neomycin Activity upon *Mycobacterium tuberculosis* and Other *Mycobacteria*, *Am. Rev. Tuberc.* 60:78-89 (July) 1949. Waksman and Lechevalier.¹

with colds, and a large comparable control group was given placebos. Treatment was not begun until symptoms had been present for 24 hours, thus no attempt was made to evaluate very early treatment. The paper statistically and graphically shows that the number of cures or improvements were almost identical in those treated and in the controls. In this study both the patients taking and the physicians prescribing the treatment and making the examinations were unaware of what medicine was being taken. The authors state: "The widespread use of antihistaminic drugs by the public, as well as by physicians, for the cure of the common cold and the paucity of controlled work in this field require confirmatory investigations under carefully controlled conditions. . . . Any form of treatment for the common head cold is influenced by so many factors that only a rigidly controlled study eliminating as many variables as possible will provide results on which relatively valid conclusions can be based.

"There was no significant difference in the proportion of cures reported by patients receiving oral antihistaminic drugs and those receiving oral placebos. Furthermore, essentially the same proportion of patients reported no benefit from either type of treatment."

The important point of this article, it seems to me, is not its results but its method. Showing that antihistamines are not the final answer for colds is important, but doing it in carefully controlled circumstances is more so. All variables were kept as constant as possible except the one being measured.

FURTHER EXEMPLARY MATERIAL

An excellent discussion of the quantitative principles in clinical research is Reid's analysis³ of the evaluation of streptomycin therapy of pulmonary tuberculosis by the Medical Research Council in 1948.⁴ They found that, in spite of many favorable reports from the United States, there had been no well controlled evaluation of this new therapy. Reid analyzes their procedure as a model in research. After the selection of a cooperative working group of scientists, the patients were separated into treated and untreated control groups. The groups were as similar as possible and were divided completely at random. He emphasizes the random, mechanical method of separation as the only means of eliminating personal bias. He states: "A notable feature of this trial was the frank realization by all concerned of the fallibility of human judgment in general and of clinical and radiological judgment in particular. . . . All judgments were made by two or more observers, independently of each other and unbiased by any knowledge of the nature of the treatment given to the patient whose physical status was being assessed. This principle of the elimination of personal bias is fundamental in all experiment, but it is of particular importance in clinical research. Thus, in the selection of patients for inclusion in either treated or control groups, the final decision was made purely on a chance basis."

These patients were followed in a routine and standardized way, with independent observers cooperating without knowledge of the patients' identity or mode of

treatment. Reid states, "The final statistical analysis by the application of the χ^2 and t tests (which conclusively demonstrated the beneficial effects of streptomycin) could thus be confidently made, since we were reasonably sure that the rain of chance events had fallen equally upon the just and the unjust. The differences observed, e. g. in case-fatality rates, between treated and control groups may be due to chance, and it is the function of the technical test of significance to test just that hypothesis. . . . Chance is always considered to be guilty or responsible for the differences until its innocence has been proved by the results of technical tests of significance. Then, and in general only then, can alternative explanations for these differences be considered. Last among these alternatives, you should consider the possibility that your own therapeutic brain-child was really producing a beneficial effect."

Such an objective approach to medical research is infrequently seen. Most experimenters have human frailties, including the desire to quickly and easily demonstrate that their pet ideas are of benefit. But we must be as skeptical of our own ideas and new treatments as we are of those of others.

COMMENT

The use of controls is frequently omitted in the evaluation of potent new therapeutic agents, such as the antibiotics. Such methods as comparison of the duration of fever in a group of treated spotted fever patients with the known duration of fever in previously reported cases are common. This type of comparison is of some usefulness, but the well known variation of virulence, of host resistance and of differences in environment, such as general care of patients, season, climate and diet, caution us to be critical. Therapeutic regimens used in diseases whose known courses are quite constant require less rigid controls for evaluation. If a new agent reduced the mortality rate of rabies from its known virtual 100 per cent to 60 per cent in a group of 10 cases, this would be of some significance even though no controls were available. However, most conditions in medicine and surgery are not so clearcut, and the more capricious they are, the more carefully we must evaluate our treatments. Again Reid states, "One must always be on the look-out for a confusion between the demonstration of a mathematical relationship and the proof of cause and effect. The association between differences in treatment and differences in outcome does not necessarily mean that the treatment has improved prognosis. The improvement may well result from some unforeseen and uncontrolled source of variation which had a selective action on one of the groups."

A recent report by Stewart Wolf⁵ reemphasizes that placebos may produce observable effects which must be remembered when drug medication is instituted. Using various substances including potent drugs and placebos on a patient with a large gastric fistula through which the gastric mucous membrane could be observed, he observed "placebo effects" which can modify the actions of drugs; at times the "placebo effects" sur-

3. Reid, D.: Statistics in Clinical Research. Ann. New York Acad. Sc. 52:931 (March 10) 1950.

4. Streptomycin Therapy of Pulmonary Tuberculosis. Medical Research Council, Brit. M. J. 2: 769, 1948.

5. Wolf, S.: Effects of Suggestion and Conditioning in the Action of Chemical Agents in Human Subjects: the Pharmacology of Placebos, J. Clin. Investigation 29: 100 (Jan.) 1950.