continuum, of course, there are cases the lesions of which show an abundance of bacilli, as the one "reevaluated" in this issue by Wade and Perrin," clinically unmistakably borderline—and, as pointed out by Meyer, of Carville, more lepromatous histologically than clinically.

We hesitate to argue here against the creation of the proposed composite group, although we fail to see the advantage of grouping true borderline cases—which are less likely to subside spontaneously, and are less responsive to treatment, than reactional tuberculoid—with those of the reactional tuberculoid condition. That would move the line of diagnostic differentiation to the zone between reactional tuberculoid leprosy and tuberculoid "reactivation," which line is not always clear-cut and certain. The matter is one for deliberate consideration and study, which it is to be hoped it will receive before the next international congress.

Another complication is presented in the thoughtful paper on dimorphous macular leprosy by Currie, also in this issue. It is only of incidental interest that, heretofore, it was his practice to refer to those cases as "borderline." He suggests that the transitional cases of macular appearance be included in the "borderline (dimorphous)" group of the Madrid classification, to be designated the "maculoid" variety to indicate that they share the essential histologic nature of the recognized borderline cases and are potentially elevated. To accept this proposal would extend the limits of the borderline group to include clinically indeterminate cases. Davison does that, including in the "borderline" group macules that are flat but infiltrated and are bacteriologically positive. This practice, fortunately, is not common. Incidentally, he has a point in requiring that borderline lesions must arise in normal skin, and that smears taken from a short distance away must always be negative.

Need one despair of unanimity in this matter "in our day"?

—H. W. WADE

12Ray Prieto, who "rejects" the term "dimorphous" in connection with borderline leprosy, believes that the dimorphous macular condition is merely a transformation phase of the indeterminate form.

TESTING OF NEW DRUGS

The issue of the Journal of the American Medical Association for July 8, 1961 is a Therapeutic Number, the first of an intended annual
edition featuring the work of the A.M.A. Council on Drugs. In the first special article Isaac Starr,¹ the chairman of the Council, relates a classical example of therapeutic error of judgment, the ideas underlying the "experimental method" involving animal experiments and experiments on man, the role of statistics, and the elimination of the personal bias of the observers by means of the paired experiment and more elaborate experimental designs—with discussion of both the advantages and the difficulties and limitations of the latter.

STATISTICS

Most of the section on statistics, which tells of what statistical analyses can and cannot do, is reproduced below, by permission.

Training in mathematics has never been a necessary or conspicuous part of the doctor's education, and one wonders how well the average practitioner is equipped to interpret the statistical analysis which accompanies the best medical papers of today. The danger is that, not fully understanding the mathematical background, doctors will attribute to such analysis virtues that it does not possess. So it seems wise to point out the difficulties and dangers as well as the advantages inherent in the statistical methods on which we have placed so much reliance in our testing of therapeutic agents in recent years.

The validity of the results secured by statistical methods depends on an assumption. For the results to be trustworthy, the variation in the data subjected to such analysis should obey the law of probability, the law which defines the expected frequency of any result when dice are cast repeatedly. Needless to say, this law does not always accurately describe the variability found in medical data; for example, it would not apply to a situation in which the magnitude of the errors in one direction exceeds that in the other. Often, when we must draw conclusions from medical data, we do not know enough about the inherent errors to make a firm judgment whether they do or do not conform to the law of probability. We usually assume that they do, and proceed to draw our conclusions on that basis. This risk has proved well worth while.

I pause to re-emphasize that statistics can never prove anything. The results of a statistical analysis demonstrate one thing only, namely, the likelihood that chance will explain the phenomena under study. If the odds are large that chance will explain what happens after giving a new drug, the drug is not worthy of further study. If the odds are large that the results cannot be so explained, the drug may, or may not, be worthy of further study. The important fact for doctors to remember is that the value of statistics is negative; it helps us to eliminate from our thoughts many things which doctors in the past thought worthy of consideration in order to concentrate our efforts in directions with greater promise of success.

There is a danger that doctors, unfamiliar with mathematical thought and methods, will expect too much of statistics. A difference between the mortality from pneumonia in patients who received and those who did not receive a new drug may be statistically significant and therefore should not be attributed to chance; however, the cause of the difference may be something other than the drug. To use as illustration a matter briefly debated at this moment, the relation between the increasing frequency of lung cancer and the increasing consumption of tobacco has proved to be significant, and one has the right to wonder whether the one is a factor in the etiuation of the other. This might indeed be true and, as the statistics indicate, the matter is well worthy of further study. But the yearly increase in frequency of lung cancer is also significantly correlated with the yearly increase in the number of automobiles manufactured in Detroit, with the

number of nylon stockings sold yearly, and, indeed, with everything else in this growing country which is increasing yearly. The demonstration that the relation between two variables cannot be explained by chance is not valid evidence that the one causes the other. Statistics never prove a causal relationship. The judgment that tobacco smoking may be a factor in lung cancer, and that the sale of stockings is not likely to be, is not based on the statistics, but is based on reasoning of another kind. I myself have stopped smoking, but I continue to buy stockings.

Nevertheless, the value of statistics to modern medicine has been very great indeed, and no modern study of therapeutic agents can be considered complete without the criterion involved in such an analysis. This rigorous criterion has caused us to prune out a great body of data which many doctors had thought worthy of attention, to the great benefit of the tree of knowledge. And the rigorous mathematical thought, which has taught us to apply the statistical method to our problem, has led to many advances.

Later, after discussing controlled experiments, he says:

[Such experiments] will permit identification of the drug which has but little benefi-
cial action, when simpler methods would fail. On the other hand, because the results of
such an experiment do not demonstrate that a certain drug exerted a "significant" bene-
}ficial effect on a series of patients, one has no logical right to conclude that it is worthless.
{Though persons of the reformer type often do conclude. When statistical significance is
not attained, the logical conclusion is not condemnation but that judgment should be
suspended. Those who insist on waiting for statistical significance before appearing
should logically wait for statistical significance, in the other direction, before condemning.

CONTROLLED EXPERIMENTATION

The author then discusses the "rough experiment" in which one-
half of a group of patients is given a drug and the other half a placebo
(or, sometimes, an established drug with which the new one is com-
peting). This experiment may suffice if the effect of the new drug is
striking, but unforeseen factors may cause so much variability as to
mask the effect of the drug. Better is the experiment in which each of
the patients is treated during alternate periods with the drug or the
placebo (which one to use first to be determined by the toss of a coin),
and calculating the differences. This type of experiment is impossible
in many types of studies. In such case matched pairs may be used for
the comparison, but again there are difficulties especially in finding
enough sufficiently-well matched pairs.

More elaborate experiments are discussed, as the "double blind"
one in which neither the patient nor the observer knows whether the
drug or the placebo is given. To find enough adequately paired patients
requires large numbers of cases, and such experiments are often set up
cooperatively in several clinics. Trained teams are needed, and these
usually consist largely of nurses and technicians. Such studies, usually
designed and presided over by a statistician, have become important in
recent years. Unfortunately, they are very expensive, very difficult to
organize, and time-consuming—also, it is very boring and unrewarding
for keen-minded physicians to do such work with no knowledge of what
is going on.

These and other considerations lead the author to suggest that the
individual physician, if trained and unbiased, may still have a place in
therapeutic research.

My expectation is that elaborate team research, despite the many advantages, will
not supplant research carried out by the single doctor, who, in the full knowledge of
what he is doing, gives therapeutic agents to patients he knows intimately and carefully
and objectively observes the effects that follow. We all know the enthusiast so biased by
his emotions that he confuses his hopes with the truth. But do we not also know the man
whose intellectual attainment has put him far above this, the man who has schooled
himself to see things exactly as they are? . . . When such a trained observer gave a drug,
and the result on his patient . . . was much different from that which his learning and
experience had led him to expect, his attention was attracted. From following up such
unexpected experiences, the profession has learned much . . . . In contrast, the elaborate
team experiment, as at present designed, diverts the attention from the unusual response,
and the man at the top who writes the paper may be altogether unaware of it. The great
therapeutic discoveries in the past have been made by competent men, not by teams
working blindly. I fully expect that this will be the case in the future.