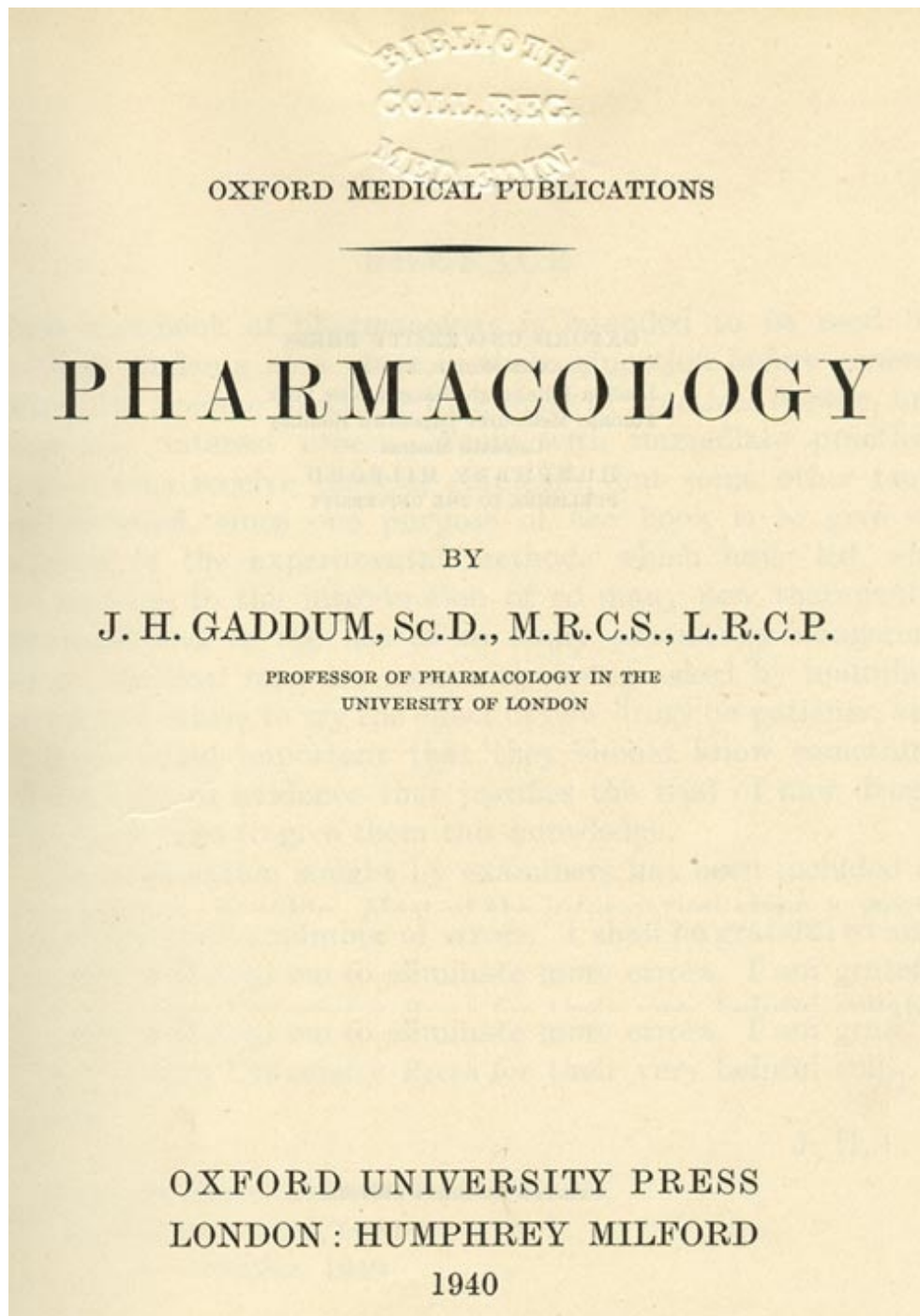


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**Gaddum JH (1940)**. Pharmacology. London: Oxford University Press, p 378-383, 1940.

**Title pages**

## PREFACE

THIS text-book of pharmacology is intended to be used by medical students at a stage in their education before general principles become obscured by a mass of practical details, but may also interest others. Facts with immediate practical applications receive especial emphasis, but some other facts are included, since one purpose of the book is to give an account of the experimental methods which have led, and are leading, to the introduction of so many new therapeutic measures and to the use of so many potentially dangerous drugs. Medical men are constantly being asked by manufacturers and others to try the effect of new drugs on patients, and it is therefore important that they should know something of the kind of evidence that justifies the trial of new drugs. This book tries to give them this knowledge.

The information sought by examiners has been included as completely as possible. Most of the information given is worth remembering, but some mathematics, chemical formulae, synonyms, and other such details have been included only for reference, or because some people like them.

I am grateful to all the authors and publishers who have given permission for the reproduction of figures. Their names are mentioned in the appropriate places.

I am also grateful to Prof. G. R. Cameron and to Doctors G. Brownlee, G. A. H. Buttle, K. H. Coward, and R. Wien, who have read parts of the manuscript, and to Doctors G. H. Faulkner and H. R. Ing who have been through the whole book and eliminated a number of errors. I shall be grateful to anyone who will help me to eliminate more errors. I am grateful to the Oxford University Press for their very helpful collaboration.

J. H. G.

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## Therapeutic Trials on Man

Experiments on man are the only kind of experiment which can give certain evidence of therapeutic action on man. Such experiments are designed to answer the question whether the health of the patients who have taken the remedy is better or worse than it would have been if they had not taken the remedy. This question is not an easy one to answer, since it is never possible to know for certain what would have happened without the remedy; patients may recover in spite of drugs or because of them. Any remedy that is used persistently is therefore bound to produce apparent cures fairly often unless it is very toxic. The wise physician can often form a shrewd opinion on the value of remedies, but opinions are not scientific unless the evidence on which they are based can be written down on paper and survive criticism. The value of objective scientific evidence of this kind lies in the fact that it represents a permanent addition to the common stock of knowledge. Subjective opinions, based on the uncodified experience of the practising physician, are often the best guide to individual treatment, but they form an insecure basis for generalizations. They are influenced to an unknown extent by the subconscious wishes of the doctor, and their authority depends too much on his individual prestige. Objective records of facts have a more permanent value, though they may lead inexperienced persons to false conclusions. Subjective opinions are usually kept in the background of the evidence, but they cannot be entirely eliminated and it will never be possible to make research foolproof.

Objective scientific evidence in experimental therapeutics depends on something, like the temperature of the patient, that can be measured, something, like death or cure, that can be classified as an all-or-none response and counted, or something, like the contractions of the uterus, that can be recorded. The methods used in the study of remedies of different kinds have been discussed in various chapters of this book, and there is not much to add to these discussions.

The proper choice of a method is fundamentally important, since the final argument usually involves the assumption that significant changes in the measured effect represent significant changes in the patient's health. The inexperienced experimenter may prove that some particular treatment increases the weight and wrongly assume that this represents an increase of health, when it is really due to obesity or oedema.

The design of the experiment may make all the difference to the significance of the final result and must be carefully considered before the experiment is started. If the advice of a statistician is likely to be needed in the interpretation of the results, this advice is more likely to be helpful if taken before

the evidence is collected than afterwards; much time has been wasted on badly designed experiments.

The evidence is usually based on the comparison of the health of treated patients with that of untreated patients, who act as a control and provide evidence of what the health of the treated patients would have been without the treatment. In some cases it is possible to make each patient serve as his own control by making observations before and after treatment. In any case, since the evidence is based on a comparison of the two groups of data, both groups are important, and a given number of observations gives the clearest results when half of them are made on treated patients and half of them are made on control patients.

The proper choice of controls may convert a vapid theory into a real contribution to knowledge; theories are cheap and ephemeral, but new facts are indestructible.

If a patient has been in a steady state, or getting worse, during a preliminary control period and he takes a turn for the better comparatively quickly after the remedy is applied, there is some reason to believe in the remedy. The strength of the evidence depends on the rapidity of the cure compared with the duration of the control period. If a patient who has suffered from myxoedema for years, and has been getting gradually worse, is cured by thyroid in a few weeks, the cure may be considered rapid enough to be convincing, but the revival of a patient who has fainted cannot safely be attributed to any remedy unless it follows within a few seconds of the application of the remedy. Remedies for chronic diseases are more easily studied by this method than remedies for acute diseases, because the control period is usually longer. On the other hand, many chronic diseases have spontaneous remissions during which the patient is temporarily much better. In disseminated sclerosis, for example, or schizophrenia or lymphadenoma or pernicious anaemia, the disease may practically disappear for months at a time. The study of cures for such diseases requires especial caution.

Evidence regarding the effect of a remedy may be vitiated by the simultaneous application of other remedies any of which may have produced the observed change. Many diseases are cured by rest in bed, and if a patient is put to bed and given

medicine at the same time, no one knows whether his cure is due to the bed or to the medicine. For this reason patients are sometimes admitted to hospital and observed during several weeks of control period in bed, before the experimental treatment is applied. The periods before and after the treatment are then compared.

Another method of using control periods is to study the statistics of a disease before and after the introduction of a new remedy. When this is applied to a whole country the results are often difficult to interpret because there are so many factors affecting the result. An increase in the number of registered deaths due to a particular disease, for example, may be due to improved methods of diagnosis, and a decrease may be due to a spontaneous decrease in the virulence of the disease.

The statistics obtained in a single hospital, on the other hand, often provide better evidence.

In all methods where control periods are used it is difficult to be quite certain that any observed differences between the patients receiving the experimental treatment and the controls are really due to the remedy being studied. Changes may occur in the cooking arrangements of the hospital or the skill of the nursing staff, or in many other factors which are unknown to the experimenter, but which happen to coincide in time with the start of the experimental period. The reliability of the conclusion that the change is not only *post hoc* but also *propter hoc* depends on the skill with which such factors are excluded. For this reason such evidence is never completely objective.

If simultaneous controls are used, it is possible to eliminate the source of error discussed in the last paragraph by selecting the controls at random. If a continuous series of cases obtained from the same source is divided into two groups so that half of them receive the experimental treatment and the others serve as controls, it is sometimes possible to ensure that the only significant difference between the two groups lies in the presence or absence of the experimental treatment. The essential point is that the cases must be selected completely at random.

The probability that the observed difference between the two groups of data would occur by chance can then be calculated by statistical methods, and if this probability is very low the treat-

ment must have had some effect. The use of random controls is almost foolproof.

If the cases arriving at a given clinic are assigned alternately to the experimental group and the control group, the grouping can be regarded as random, provided that the decision to include each case in the whole series is made by someone who does not know whether the case will be a control or not. Otherwise there is a danger that he may tend to include mild or doubtful cases when he knows that they will be in one or other group, and so tend to produce the result which he subconsciously desires. Methods of randomization depending upon the tossing of pennies and other such mechanical devices are preferable.

It is always necessary to consider the possible effects of suggestion, which may play a very important part in therapeutics. The patient who has faith in the treatment he receives is more likely to recover than the patient who has no faith, and inert substances may cause dramatic cures if used, in appropriate cases, with suitable suggestion. Cures due to suggestion are, of course, in no way less creditable than cures due to drugs, but unless suggestion is excluded from experiments on the action of drugs, it is often impossible to know whether the result was due to the suggestion or the drug. Suggestion cannot affect the result if the patient does not know when the treatment starts or whether he belongs to the control group or the experimental group. For this reason it is often best that all the patients should appear to receive the same treatment all the time that they are under observation, but that the pills, mixtures, or injections administered to the control group should not contain the active ingredient whose effect is being studied.

The actual carrying out of the experiment is often difficult. In studying the effect of milk on schoolchildren it is easy to give milk to all the children in one school and to keep another school as a control, but such controls are not random, since the relative health of the two schools may be affected by many factors besides the milk. On the other hand, if controls are really random, the experiment is likely to be complicated and to lead to jealousies.

The conclusions are, strictly speaking, only valid when the experiment is carried out exactly according to the design, without exceptions for special cases, and this is sometimes difficult

to do. It is almost impossible to apply the method of random controls to diseases with a high mortality, because the doctor does not feel justified in withholding a remedy which may possibly save lives from any of the patients, even when he does not know definitely whether it is effective or not. On the other hand, it is important to remember that new medicines are often toxic, and may make the disease worse. The maximum number of lives will probably be saved if the true facts are established as rapidly as possible.

The methods of determining the significance of the evidence are similar to the methods of calculating the result of a biological assay, but simpler, since quantitative results are seldom sought and definite evidence that the treatment is either a good thing or a bad thing is usually enough. Large numbers of uncritical observations are not necessarily more significant than a small number of carefully controlled experiments. Observations on a dozen treated patients and a dozen random controls may be much more convincing than a series of many thousands of cases with no controls, or even with control periods. If the data are in the form of some quantitative observation, made on each patient, such as the duration of his stay in hospital, the mean value for the treated and control groups is calculated and the significance between the difference of these two means is estimated by the method given on page 361. If the results have been obtained by counting the number of patients cured, they can be expressed as percentages, and it is then sometimes obvious whether the difference between the two percentages is significant or not. If there is any doubt on this point, the question can be decided in the following way:

Let  $a$  be the number of treated patients cured, and  $b$  the number of treated patients not cured. Let  $c$  be the number of control patients cured and  $d$  the number of control patients not cured.

Calculate  $\chi^2$  (chi squared) from the expression

$$\frac{(ad - bc)^2(a + b + c + d)}{(a + b)(b + c)(c + d)(d + a)}$$

The probability that random differences, not due to the remedy, would make  $\chi^2$  as large as 3.8 is 0.05, or in other words if  $\chi^2$  is greater than this, the odds are at least 19 to 1 that the remedy had some effect. If  $\chi^2 = 6.6$  the probability is 0.01 and the odds are 99 to 1. This formula is only accurate when the numbers involved are large; there is no simple way of working out the odds accurately when the numbers are small.