

*Lectures on the
Methodology of
Clinical Research*

MAX HAMILTON

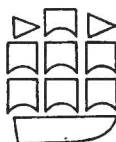
Lectures on the
Methodology of
Clinical Research

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PREFACE TO THE SECOND EDITION

Books, like human beings, grow larger as they grow older: this is unfortunate, but it cannot be helped. This second edition is bigger than the first but the growth is a compromise between the need to keep it as small as possible and the request of many readers to add more material on the practical aspects of research and on statistical calculations. I know that I have omitted many important themes, but decisions had to be made and I can only hope that they have been the right ones. Fortunately, it has been possible to introduce some modern notions in statistics without adding further to the size of this edition and I would like to think that the changes have increased the book's value to beginners in research without adding to their burdens.

I would like to thank Mrs. Betty Barnes for the typing of the manuscript and also Dr. Ken Warren and Mr. Colin Pritchard who acted as "guinea pigs" and made some useful comments on the clarity of the text and some suggestions for the glossary. Finally, I would like to acknowledge the help given to me by my Assistant, Mrs. Joy M. Brierly, in the preparation of the manuscript, for the proof-reading and indexing and also for help with the calculations.

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MAX HAMILTON

LEEDS, 1974

PREFACE TO THE FIRST EDITION

Medical post-graduates can constitute the toughest audiences that a lecturer may meet. It is my experience that they are of high ability, have a good background of science, and because of their training in the art of interviewing patients, tend not to be over-awed by a lecturer. I am sure that this contributes to their sophisticated and even cynical attitude to lectures and lecturers. In direct contrast to this is their rather naïve attitude which tends to put at opposite poles the science of medicine, by which is implied laboratory work and diagnostic machinery, and the art of medicine, which is essentially regarded as clinical judgement, based on experience. If this remark seems exaggerated, it will be amply confirmed by a perusal of medical journals, wherein will be found articles and lectures in which the art of medicine is counterposed to the science. But there can be no doubt that clinical practice needs much more science than it has had heretofore. It is not sufficient for the clinician to rely on his empirical "experience" and ability to understand the patient as a human being, leaving the "science" to specialists and technicians. This can lead to one end only: the disappearance of the clinician (who sees the patient as a whole and treats him as a person), and his replacement by a group of specialists, who are interested primarily in their speciality.

It is on the basis of this opinion and with this particular audience in mind that I designed this set of lectures and gave them first in 1953. The lectures have been repeated annually, and among those who have attended regularly have been physicians, surgeons, obstetricians, anaesthetists, clinical pathologists and psychiatrists. That I have been able to retain their interest is sufficient proof that the lectures were useful. On a number of occasions I have been asked to publish these lectures, but have refrained from doing so on the grounds that there were many good books already available on the subject.

Recently I have been "going through the literature" and have been surprised how many books there were, and how very good they were. It is true that the number that deals directly with problems of clinical medicine is small, and it can be said of many of them that they are very much concerned with statistics as such

and the details of computation. Books on the design of experiments also tend to be difficult. Perhaps there is room for a small book, one that is concerned primarily with clinical problems and concentrates on the logic and principles of the application of science to clinical research.

A word of explanation for the title: of course, these "lectures" are not transcriptions of the lectures as given. The conversational and colloquial style of speech appropriate to a small audience is quite unsuited for writing. So also are those pleasantries and asides which give an audience a moment's rest and renew its concentration. The questions and discussions which interrupt a lecture, and which are so important for making the hearers active participants in the process of learning instead of mere passive recipients of information, have perforce been omitted. Nevertheless, there are good reasons for retaining the form of "lectures". The first is that it is made clear that this work is not intended to compete with the many excellent text-books. Lectures should never attempt to do what can be done by a text-book; their prime function is to give students help and guidance in the use of text-books. The second reason is that thereby I can retain the original "spiral structure" of the lectures: the return, again and again, to the same themes, but each time at a higher level. Such a structure is particularly suited to an elementary course of lectures, but is inappropriate in a book which will be used not only for instruction but for continued reference.

For any merits that this book possesses, I have to thank two persons in particular. First, Emeritus Professor Sir Cyril Burt, of the Department of Psychology, University College, London, for not only did he introduce me to scientific method, but he was the first of my teachers to demand high standards of me. Second, Dr. Ardie Lubin, of the Walter Reed Army Institute of Research, Washington, D.C., whose eminent use of the Socratic method has forced me to try to think clearly. There are passages in this book which remind me of particular sessions with him, stimulating, exciting, but very strenuous. I would also like to thank Miss M. Knott for her care in the preparation of the script and help with the index, and Miss E. Read, B.A., Librarian of the Leeds Medical School, for help in finding some of the references.

MAX HAMILTON

WAKEFIELD, 1961

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Introduction: Structure of a Research Project

These lectures are entitled 'Lectures on the Methodology of Clinical Research'. Let me explain this. In the course of these lectures I am going to give an account of the underlying principles and methods of thinking involved in doing clinical research. I shall try to explain how one formulates a clear question and then designs an investigation to obtain an answer. This means, in practice, designing a procedure for yielding appropriate data and drawing inferences from them. This, because of the variability of biological material, requires a statistical analysis. I shall try to show that the techniques of statistical analysis are merely a particular way of drawing inferences from data. To the beginner, this appears to be a formidable task but I hope to demonstrate that the essence of the designing of clinical investigations and the analysis of the resulting data is a comprehensible logical process.

It is an interesting experience to examine a very old copy of a medical journal: the general appearance is quaint and even amusing. For example, that very respected British medical journal, *The Lancet*, first came out in pocket magazine size—diminutive medical journals are not at all a new idea—and its contents, to the modern reader, are astonishing, to say the least. They consist very much of medical news and accounts and reports of lectures, the latter containing a surprising amount of personal anecdotes. There is sometimes a vague air of the newspaper advertisement about these lectures 'I did the following and the patient was cured'.

The contents of a recent number of a general medical journal are very different indeed. Most of the material in the journal is a description of original research work, a good deal of which consists of biochemical, physical and chemical investigations, with a sprinkle of clinical ones. Of the last group, the great majority consist of 'clinical trials'. These consist of carefully planned investigations to evaluate a treatment and the result is usually expressed in statistical terms. Many others are concerned with prognosis and the determination of prognostic criteria. Others are concerned with

refinements of diagnostic techniques. All of these papers use statistics to describe their results, even if these are at the lowest level of mere proportions or percentages. The emphasis is on the use of scientific methods for the increase of knowledge, and the change in these medical journals reflects an important change in medicine.

In the past century, the art of medicine has changed largely from a traditional craft to an applied science. All of us who are engaged in the practice of medicine have a duty to our patients, to do the best we can for them, and this requires not only that we should understand the new developments but also to some extent that we should contribute to them. For the best way of understanding what is new in medicine is to take part in it. It is for this reason that so many young doctors are now enthusiastically interested in or trying to do research. The same can be said for associated professions, e.g. social workers and nurses.

Motives for Research

It is easy to be very cynical about this and to believe that the only reason why doctors, particularly young ones, are engaged in research or express an interest or an enthusiasm for it, is that they do so in order to advance themselves in their professions. The interest is not in research but merely in 'getting on'. This sort of opinion, it seems to me, is not so much cynical as silly. All young doctors have to make their way, and they do so by securing the approval of the older and more senior members of their profession. They do this by conforming to what is regarded as the right and proper way of doing things. When the proper way is the practice of medicine that is what they do; and when it is research, they do that. In America, if one wishes to become a Professor of Psychiatry, almost invariably it is necessary to undergo psycho-analysis; so young psychiatrists get themselves psycho-analysed. In other countries this is a very undesirable thing to do, so they don't. In the 17th century, the aspiring English physician paid a visit to Italy, in the 19th he went to Germany and nowadays he goes to the United States.

The motives for research are a personal matter and of little concern to others. What matters is the result, the research itself. There are only two kinds of research, not those with good or bad motives, but just those that are good or bad. It is true that many doctors express a desire to do research only because they think that

if they publish enough papers they will get better jobs. It seems to me that this could be as good a reason for doing research as any, but the man who boasts of a long list of second rate papers concerned with trivial matters, condemns himself in the eyes of his peers. If he wants to make a name for himself he can best do so by trying to do good research.

There is also another good reason for trying to do good research. There is no point in doing research unless it is published. The number of papers offered to journals is steadily increasing. It is increasing, believe it or not, even faster than the number of journals and this means that the pressure on editors is rising. The selection of papers for publication therefore becomes steadily more intense. If you want your paper to be published, it had better be a good one. I won't discuss other motives, such as the satisfaction obtained from doing good work and from playing one's part in the advancement of medicine. Surely these go without saying.

Even if we are not likely to be involved in research, we still have to understand what it is all about. We are all 'consumers' of research, even if we are not producers. At the best, we want to keep up-to-date with judgment and discrimination. At the worst, we shall quickly find that the investigations and treatments we order for our patients cease to be available.

Research and Clinical Practice

It is often said that good clinical practice is incompatible with research, or at least that the attitude of the clinician prevents him from taking part in clinical research. I disagree with this completely. No clinician can rest satisfied with present-day therapies. Every one concerned with sick people is delighted when a patient recovers and even more so when he has good reason to believe that it is his intervention which has produced the recovery; but that is not enough, he should also worry about the failures of treatment and these should be his constant preoccupation. The aim of medicine is, ideally, to prevent disease and when this fails, to cure it; but from where does the knowledge for this come? Everyone will agree that for proper diagnosis and treatment, a good clinical history is fundamental. Surely this provides the data for hypotheses concerning the causation of the patient's illness? The clinician cannot shut his eyes to this. Even at this most basic level, good clinical practice provides the data for research.

A doctor should give his patient the best treatment that he can. But what is the best? Presumably it means the treatment which will give the best result for the particular patient. How can this be known without careful study of the factors in the patients' condition and in their history and background which are related to the outcome of a particular treatment. Here again is the basic material for clinical research.

It is a tradition of medicine that doctors should try to use a new treatment if there is evidence which suggests that it is better than the old. But what is evidence? Traditionally, it is the say-so of 'authorities', but we know only too well from the history of medicine that this is just as likely to lead to the introduction of useless and even harmful remedies as lead to good ones. When the physician tries a new remedy, surely it is worth his while to try to collect the evidence that will demonstrate its superiority to the old treatment. The cautious physician sticks to the old and may thereby find himself depriving his patients of the benefits of the new. The enthusiast swings over to the new and may find himself exposing his patients to dangers. Neither of them can contribute to new knowledge and therefore to improve our methods of treatment. It is the intermediate approach which does so. A gradual change over from the old treatment to the new means that some patients are receiving the old treatment and some the new and this is clearly the basis of the modern clinical experiment with its control series. Such a cautious approach can be carried out even when a physician is trying a new treatment for the first time. Obviously he will try it on those patients who have failed to respond to traditional treatment. In doing so, he does not deprive them of the full benefits of what is already known and yet gives them a second chance to benefit. Once the physician has gained experience with this treatment and finds that it is not unsatisfactory he can then extend its use by giving it to those patients whom he would expect to be failures of treatment. The third stage is obvious, when he starts to give it to the general run of patients but always remembering to compare the new with the old in proper fashion.

The Structure of a Research Project

A good way to begin is to consider the structure of a published paper describing a piece of research. If you understand this clearly it will also help you when you come to write up your own reports.

It is often complained of such papers that they do not really give an account of how the work was carried out. There is no description of the struggle to define the questions, to develop a satisfactory method of investigation and to overcome the practical difficulties that were met. There is nothing about the false starts and the trails that led nowhere. There is a good reason for this: such matters are largely of personal interest. Perhaps the biographer of the researcher, or the historian, might be interested in them. The purpose of a scientific report is to give the reader information of two kinds. The first is concerned with the actual findings and the second with the background which enables the reader to evaluate them.

A research paper can be divided into six sections. They are:

1. Review of the Literature.
2. Statement of the problem.
3. The method of investigation.
4. The results and the conclusions.
5. Discussion of the results.
6. Summary.

REVIEW OF THE LITERATURE

When you start to read a paper, having first read the title, you will at least have some notion of what it is going to be about. The purpose of the review of the literature is to give detailed information about the subject. It will tell you what has been done in that field of study and also, ideally, it will tell you what has *not* been done. It will give an account of the background of the subject and will do all this in a critical fashion. In other words, the author will explain the value of the work that has been done, describing those researches which have achieved something and those which are inadequate in the way they have been carried out, and giving the evidence to demonstrate this. Above all, the review of the literature should explain to you why the subject *matters*. Ideally, when you have finished reading the review of the literature you will not only have a fair notion of what the problem is all about but what will be the nature of the investigation to be described in the paper and why it should have been undertaken.

I am always very suspicious of the review of the literature which is uninformative and which gives a large number of references. 'The factors affecting the concentration of this constituent of the blood have been investigated on a number of occasions (1), (3), (5),

(7), (9), (11). Some of these findings have been accepted (4), (6), (8), and others have not been confirmed, (10), (12), (13), (14).' When I read this sort of drivel I have a strong belief that the writer has not actually read the works to which he refers, but has merely copied out the names from some other paper, and I will need a good deal of evidence to convince me that this is not so. Sometimes, such lists of papers are amplified by brief statements about their contents, but bitter experience has taught me that such descriptions can be misleading. Careful examination of the papers referred to has sometimes shown me that the writer referring to them has read only the summary, because the summary differs from the content of the paper. I remember one paper in particular that was referred to repeatedly for many years and was stated to have proved that the response of some patients to psychotropic drugs depended upon their environmental circumstances. Careful reading of the paper itself demonstrated only too clearly that the authors had considered that this might be a possibility but one which did not even arise from the data in the paper. The function of the review of the literature is to inform the reader rather than to advertise the writer.

At this point I would like to mention that the structure of a paper published in a journal is exactly the same as the structure of a thesis for a higher degree. The essential difference is simply the amount of space available. The investigator who writes a paper for publication in a journal will generally cut it down to an irreducible minimum; if he doesn't the Editor will. When an investigator writes a thesis he does not have to worry about considerations of space. He can afford to spread himself and to discuss matters in detail. This applies particularly to the review of the literature. So, for those of you who are contemplating doing a piece of research for a thesis, I would like to give you some advice concerning the writing-up.

When you write the review of the literature, you should give plenty of quotations and when you give an opinion or an evaluation of a particular piece of work, you should always back it with the evidence required. You should give your reader all the information necessary for him to accept your conclusions about the content and the value of the paper. You should not hesitate to compliment or to criticize adversely any particular investigation. Fortunately, since most theses are not published, they can be considered as semi-private documents and you do not therefore need to worry about being tactful about bad work or a fear of the possibility of a libel

action. Ideally, your reader should be given all the information required about the paper you are discussing. The only reason why he should need to go and look at the original paper itself is to check whether in fact you are telling the truth; certainly not because he cannot understand what you have written.

STATEMENT OF THE PROBLEM

If the review of the literature is adequate, then by the time the reader comes to the end he should know exactly what the problem is and have a shrewd idea of how it should be investigated. The simple statement of the problem makes this perfectly clear. There are two ways of describing the problem: either as a direct statement, e.g. 'This investigation is concerned with whether . . .', or in the form of a question. The purists prefer the latter form and with good reason. If you are going to put yourself to a good deal of trouble to collect data to answer a question, you might as well ask the question clearly at the beginning. Speaking personally, either way is equally good. All that matters is that the reader should be perfectly clear about the nature of the problem. There is one method of stating the problem which should *never* be used and that goes—'The following investigation was designed to disprove the null hypothesis that . . .' There was a fashion for this in psychological journals at one time and I could never understand how the Editors could pass this silliness. Incidentally, the statement of the problem should be accompanied by such definitions of terms that will clarify ambiguities and explain unfamiliar terms. I remember reading a paper on 'unstable angina' which never condescended to explain what the term meant. In a journal of cardiology this would be acceptable, but this paper was in a general medical journal.

. . .

METHOD OF INVESTIGATION

The next part of the paper describes the method of investigation. Strictly speaking, this section of the paper should describe the whole procedure in complete detail. In practice, this is not possible and very often not really desirable. If standard tests, biochemical, physiological or psychological, are used, then there should be no need to describe these in detail. The readers can reasonably be expected

to know what they are. At the most, a reference to the original descriptions should be sufficient. If non-standard or new tests are used these should be described in sufficient detail. If full details have already been given in a previous publication, these can be referred to but a good paper will, even in these circumstances, give some account of these new and relatively unknown tests. This is the sort of thing that the reader wants to know and the way in which it is done shows the judgment of the writer.

Then follows the design of the experiment and a description of the 'material' on which it was carried out. If it is a biochemical investigation carried out on bits of tissue, then the method of preparing them will be described. If it is an experiment on animals, then the type of animal will be defined. If the investigation is carried out on patients suffering from a given disorder, then the diagnosis will be given in sufficient detail to make clear to the reader what sort of illness it was. Furthermore, the type of patient should be described properly. What this means depends very much on circumstances but the essence of this description is that the group of patients on whom the investigation was carried out should be described in such a way that they are identifiable. The report of an investigation is, in a sense, an historical document. It describes what was done by the investigator and that is something that happened in the past. It is of interest to the reader chiefly because it serves as a guide to action in the future. If the paper describes the result of treatment, you will want to know whether this treatment is worth using and therefore you will want to know to what sort of patient it should be applied. If this is not given clearly in the paper then obviously the rest of the information in the paper is useless.

RESULTS

By the time you reach this point you may have come to the conclusion that the investigation was carried out so badly or so pointlessly that you are not interested at all in whatever results were obtained. In that case, you will pass on. If, however, you are still interested, you will now expect to read a description of what was found. The findings are generally expressed in statistical terms and these are of two kinds—descriptive statistics and evaluative statistics. The latter are the tests of significance and I shall describe them in detail later.

DISCUSSION AND SUMMARY

In the discussion, the author takes his results and puts them against the background which he has described in the first part of the paper. He considers in what way his findings are in agreement with those of others and in what way they differ and he goes on to consider what these resemblances and differences signify. If his findings have any relevance to theoretical problems, he will then go into this.

If the Editor of the journal has given the author sufficient space, he will then go on to consider the merits and demerits of his work. This has two aspects; the first is concerned with what has or has not been achieved, by his investigation; the second is concerned with the success or failure, in the sense of limitations, of the investigation. Finally, the author will then suggest in what way further work can develop from what he has done.

The summary is the first thing that the experienced reader will turn to when he has read the title of the paper, and for this reason it has become customary in recent years for the summary to be placed above the main body of the paper, with special emphasis on the results and some brief statement about the method. Although the summary should be brief, it should also be informative. There are few things I find more exasperating than the sort of summary which states 'an investigation into certain problems has been described and the results listed'. This is about as useful as a sick headache. The summary should be accurate and I regret to say that this is not always so. I never know whether to be amused or annoyed by this, but it is well you should remember it when you have need to look up references.

Summary

In this lecture I have given an account of the structure of a research report published in a medical journal. This structure is important not only because that is the way one should write a paper, but also because it reflects the structure and procedures of the research itself. It therefore gives, in outline, an introduction to the various stages of a research project.