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OPPORTUNITIES FOR RESEARCH IN GENERAL PRACTICE*

BY

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It has always seemed to me a pity that our three leading medical journals which deal with general medical topics as opposed to specialties—namely, the *British Medical Journal*, the *Lancet*, and the *Practitioner*—contain so few articles by general practitioners. It has also seemed to me a pity that those who have facilities for research usually have little access to, or little interest in, the common afflictions of the people, whereas those who have access to and experience of the common afflictions have little time or opportunity to study them.

An Attitude of Mind

To some extent this is both the result of, and responsible for, certain common misconceptions about research. The conventional picture of the research worker is that of a rather austere man in a white coat with a background of complicated glassware. My idea of a research worker, on the other hand, is a man who brushes his teeth on the left side of his mouth only so as to use the other side as a control and see if tooth-brushing has any effect on the incidence of caries. In other words, I am speaking of research not as a career but as an attitude of mind.

Anyone who has to read, as I have, many medical papers which are rejected, as well as many which are published, must realize that a number of people doing research at the present time have little aptitude for it, being sterile of ideas and lacking in the simplicity of approach to a problem which is so often the mark of a good piece of work. The idea of "doing some research" has come first, the finding of a problem second. Ideally it should be the other way round, though I admit that one must first get rid of the misconception that research can be done only by people specially paid and equipped to do it.

When doctors come to ask, as they occasionally do, whether they could work towards an M.D. thesis, this wrong attitude to research is frequently displayed. Research, to their minds, means doing some laboratory test, so they have thought out some slight modification of some simple test which they contemplate trying out in 100 patients; for instance, doing sedimentation rates on people with migraine. Now, this type of thing is rarely worth doing at all, and, if it is, it could be done better in a hospital by technicians than in general practice. Far better as a research worker is the man who

cleans his teeth only on the left side. He has a problem to solve, and an important one, and a simple way to solve it. If he has been badly educated in elementary principles he might clean only his top teeth and not the bottom ones; but that would admit a possible error of selection, for the top and bottom sets, being morphologically different, may differ inherently in their resistance to disease. If he is a really good worker, on the other hand, he will urge his brother—preferably an identical twin—to clean only the right side and compare results. You may well ask why I have not made this simple experiment myself. The answer is that when the idea arose recently out of a conversation with Dr. Margaret Roscoe in my department it was already too late.

A Wartime Experience

Before going further I would like to speak of an experience which I think illustrates some of the points that I wish to make. Towards the end of the Tunisian campaign, about April or May of 1943, I was in a general hospital very near to Tunis. When the epidemic of bacillary dysentery broke out with sudden violence among British, Free French, American, German, and Italian soldiers alike, we were of course immediately flooded with cases. Practically the whole hospital became medical and practically every ward became a dysentery ward. We had no nurses or sisters, only nursing orderlies, many of whom had had the scantiest of training. The hospital had been hurriedly erected, conditions were extremely primitive, flies were so prevalent that you ate your food with one hand while flicking off the flies with the other. Many of our medical officers themselves developed dysentery, and those who remained on duty were therefore grossly overworked. Sulphaguanidine was new and was in short supply, so that we could not use it for more than about a third of our cases. These seemed to me to be ideal conditions for a bit of research, for I had long wondered if the traditional treatment of dysentery by sodium and magnesium sulphate had any advantage over simple rest in bed and a fluid diet.

Conditions were ideal for four reasons. First, the number of cases likely to be treated personally in the next few weeks was going to be very large, and therefore statistically significant results would be obtained. Secondly, since the evidence would all be compiled in one epidemic it would eliminate errors due to treating cases at different times and under variable climatic

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and geographical conditions. Thirdly, sulphaguanidine, which was likely to prove very beneficial, was in short supply and so no ethical problem arose of the justification for withholding it from one batch of cases. Finally, the population to be studied, being a military one, did not show the variations in age, sex, and occupation usual in civilian practice.

The sergeant dispenser was instructed to make up a special dysentery medicine, which was in fact a placebo containing colouring and flavouring matter. Patients were divided into three groups. One group had sodium sulphate, another had the special mixture, and the third had sulphaguanidine. Cases were unselected, and were put into groups according to their order of admission, with the exception that any case whose illness was deemed to be unusually severe or dangerous was put into the sulphaguanidine group. Since this group was likely to behave best, this acknowledged error of selection would weight the evidence in a direction unfavourable to the probable result, and so was permissible. This part of the planning took perhaps half an hour. It remained to decide what were the simplest criteria on which to judge results with the minimum of time consumption—for instance, diarrhoea, blood in the stools, pyrexia, and so on. But as one would not allow a man to get up from bed until blood in the stools, gross diarrhoea, and pyrexia had ceased, it was really enough to take the time from admission to hospital as a fresh case (not a transfer) until the patient was allowed to get up. To note this in a book in which the three groups were recorded, without respect to name, rank, or age, was therefore all that was necessary.

The answer was clear-cut. Sodium sulphate was no better than the placebo treatment, if as good; but the sulphaguanidine group fared much better than either of the others in spite of being unfavourably loaded by containing the more severe cases.

Making Use of Opportunity

Now, I quote this in the first place to take the wind right out of the sails of those who say they have no time to do research; secondly, to show the importance of planning in advance; and thirdly, to show the importance of making use of opportunities.

There may be some who think that giving sulphonamides early in influenza prevents complications and shortens the illness. It could be proved one way or another in the next influenza epidemic if plans were ready. No hospital in the country can do it. Of course, in general practice, with patients varying widely in age, it would probably be necessary to take account of age and sex, but the patient's card would give this information and you need only put down S for sulphonamide case, A for aspirin, if that is going to be the alternative, and a number to represent days in bed, and another number to represent days off work. Treat cases alternately with one method or the other, and when the epidemic is over and there is an hour or two to spare add up the figures and publish the results. They might save the country thousands of pounds in sulphonamides or, alternatively, thousands of man-hours by returning workers earlier to their occupations. Of course, as in all experiments, something quite unpredicted might come out. Careful analysis might show, for instance, that, whereas in nine cases out of ten the alternative drugs made no difference, there was a small group which did particularly well (or badly) on sulphonamides. This might lead to further research to see what were the factors involved in this unexpected result. In this way one becomes led on from one problem to another, and perhaps only rarely ends by discovering what one set out to find.

The Statistical Method

Research is worth doing even if the results are never published; it gives personal satisfaction and makes work more interesting, more accurate, and more efficient. Research on common diseases in general practice could be of at least two kinds—the short-term acute research such as that outlined, or the long-term one. Both need planning in advance. In the short-term experiment one would choose an epidemic in which there would be enough cases for statistical analysis to be relatively unimportant. In a long-term experiment statistics would have to be considered from the beginning. Statistics is a subject about which people have views or by which they may be frightened, and it is not unusual for them to conceal their fear beneath a bold contempt. "Statistics can prove nothing," and, "Statistics can prove anything," are the two opposing statements often uttered. Statisticians don't attempt to prove anything. They merely apply a mathematical test to the results which will tell whether they are likely to have occurred by chance or whether they are much more likely to be explained by some real difference of circumstance between the groups being compared.

A good deal of the research which could be done in general practice is bound to be statistical in nature, though that does not imply that you need to be a statistician to engage in it. Much of what statistics can show is common sense and is obvious to any critical worker, but a grasp of the first principles of statistical method will often avoid falling into a number of errors and fallacies, and it is nowadays fairly easy to obtain help from an elementary textbook or from someone statistically minded, when necessary. Clinical research often consists in the comparison of one group of cases with another group of cases differently treated, as in the influenza and dysentery examples, or the comparison may be made between the group studied and the known behaviour of the illness under consideration. For instance, if you have a new way of managing cases of coronary occlusion which you hope will reduce the mortality, you can either treat alternate cases and compare the treated with the control group, or you can, in an instance such as this, treat all cases and compare the results with the known mortality from coronary occlusion in series of cases published by other authors. Of course research need not be therapeutic; the incidence of osteoarthritis in heavy workers might be compared with the incidence in sedentary workers or in the population at large.

Value of Statistics

The statistical side of the problem should usually have some consideration before an experiment is started. Suppose the mortality from coronary occlusion in cases not immediately fatal (obviously these would have to be excluded as they could not be treated) is known to be 25%. Suppose you treat ten cases and all but one recover, your mortality therefore is 10%, whereas the general mortality is 25%. This may seem convincing, but statistics will tell you that it could happen in about one in four of such trials by pure chance. It is in fact a good deal more likely than picking up a bridge hand with two aces in it (which happens about once in five hands), and no one would consider that worth writing to the *B.M.J.* about. Statistics can tell you that if your results show a 10% mortality and the general death rate is 25% you would need to have about 35 or more cases for the results to be significant. What we term statistically significant is a purely arbitrary standard, the usual one accepted being that the result would occur by chance less than once in twenty trials. If you need 35 cases to make the results above the likelihood of chance, and you see only about five cases of coronary occlusion annually, obviously this bit of research is going to take seven years. Surely this is a piece of information worth knowing.

It is quite true that statistics can prove nothing. The fact that results are not significant does not mean that your

new treatment is no use; it may be, or it may not, and if the trend is in the right direction it is worth while to continue and to record a larger series. On the other hand, if the results are significant statistically it does not prove that it is your treatment which is making the difference. It still might be due to chance, though that is unlikely, or it may be due to other factors which have not been controlled. Here we come to what statisticians call errors of sampling. If you are to compare one group of cases with another, it is essential that, so far as is possible, they should be the same in all respects except for the difference which is being studied.

A paper which I had to read recently gave the ratio of male to female cases in a certain type of cancer as about 5 to 2. The ratio was compiled from about 60 post-mortem examinations and would therefore appear to be significant, but the author omitted an essential piece of information—namely, the sex ratio of all post-mortem examinations over the same period of time at that hospital. For the hospital might contain far more male than female beds, or, alternatively, the house-physician might have found it much easier to obtain permission for necropsy on his male patients. For reasons of this kind it is often much more difficult to do clinical research in hospitals, especially in very specialized ones, where patients are highly selected before ever being sent to hospital; and there are undoubtedly many problems, as we shall see later, which can be solved only in general practice. But even in general practice errors of selection or sampling are bound to occur, and one must always be on the lookout for them. It would, for instance, be unwise to come to any conclusion on dietetic habits of the population if your practice is largely confined either to the well-to-do or to those in the lower-income groups.

In any case, results must be interpreted with full allowance for all the possible factors involved irrespective of their statistical significance, and, especially in writing up the results for publication, it is most important to separate fact from inference. It may be a fact that one group of patients has recovered more quickly than another; as to what are the causes of the difference is for you or for others in full knowledge of the circumstances to infer. Obviously the inference may be wrong even though the facts are incontestable.

Some Suggestions

That is all I want to say on methods; now for a few suggestions on subjects for research which might be studied in general practice—many of them could be studied only in general practice. Subjects which should be suitable are the incidence of certain common disorders in the population—what proportion of people suffer from migraine, for instance; the influence of occupation, social conditions, and heredity upon common ailments; and the treatment of complaints, including neuroses. Here are a few specific suggestions. I have often been impressed by the frequency with which patients with hypertension will give a history of having had migraine in the past. Whether this is pure coincidence because hypertension and migraine are both common disorders, or whether the two complaints are related, or whether hypertension is more likely to be discovered because the patient complains of migraine, I do not know, nor can I find out, for the people I see are highly selected, usually because of the severity of their complaint or because of its resistance to treatment. If we knew the incidence of migraine in the general population of persons who visit doctors, and in the hypertensive population, or if we knew what percentage of sufferers from migraine had blood pressure above the average, we would have the answer.

Physicians, having seen a case of effort syndrome or aerophagy, for instance, after taking reasonable precautions to exclude organic disease, usually recommend explanation and reassurance. Does it do any good? What are the results of a follow-up of such patients when half have been treated by simple psychotherapy and the other half by bottles of medicine for indigestion or palpitation?

Rheumatic complaints: how many fit into a recognized pattern such as osteoarthritis, rheumatoid arthritis, displaced disks, occupational strains, and neuroses? How many are left which cannot be so classified? Is there such a disease as fibrositis? In questions such as these some radiological and other expert help may be required, but there is little doubt that it would be forthcoming if the case were sent for a hospital consultation where necessary, so long as the requests were reasonable.

It is well recognized that an important cause of hypertension and of renal failure is pyelonephritis. In hospital we see only the cases that go wrong, and they are probably only a small minority. What percentage of patients who have a urinary infection later develop these complications? Again it is a question which can be answered only by general practitioners. Perhaps the cases in any one practice would be too few to give the answer in a reasonable time; if so, several doctors could combine to make a survey of their patients. This type of research would certainly need a little extra work, but not necessarily very much. It might be done by confining one's interest from a research point of view strictly to the one subject. It is rarely possible to be investigating two subjects at the same time. In all cases of cystitis or pyelonephritis the blood pressure would be recorded and the urine would be examined for pus cells as a rough confirmation of the diagnosis. A special mark would then be put on the patient's card. This might, I suppose, mean an extra twenty minutes' work every few weeks. In times of stress cases might have to be omitted from the series. In a few years' time an effort would be made to re-examine all the cases in which a urinary infection and blood-pressure reading had been recorded.

Sciatica is another subject for research. The orthopaedic surgeons in hospital practice see only a highly selected population and are in danger of assuming that all cases of sciatica require a laminectomy. But I seem to remember that before displaced disks were recognized one did not see a large proportion of the population hobbling about with incurable sciatica. What proportion of cases recover quite quickly with simple conservative treatment? Again it is a problem which can be answered only by general practitioners.

Do people with a tendency to obesity have a predilection for certain foods? Would it be worth while preparing a list of foods, including delicacies such as cream buns, and asking thin and fat patients to mark honestly the foods which they like very much, like fairly well, tolerate, or avoid? Speaking of obesity, I commend the article by Edwards and Swyer (1950) to all practitioners. These authors, by a very simple piece of research which could easily have been done in general practice (but was not), showed that dextroamphetamine had a highly significant effect as an adjunct to a low-calorie diet, whereas thyroid extract, which had been used for many years, had none at all.

Does having baths have any bearing on the liability to skin complaints? Will frequent scrubbing of the fingernails prevent the spread of boils? Does a furred tongue indicate any recognizable state of health or is it associated with dietetic fads? Are cough medicines other than sedatives any use? Or would the chronic bronchitic be just as satisfied with gentian and soda?

Therapeutic Experiments

In questions of therapy, ethical considerations may arise. Obviously it would not be right, for instance, to withhold penicillin from cases in which its efficacy is already proved, but many of the common minor ailments are either trivial or self-limiting, or are known to be little influenced by treatment.

Professor Pickering once remarked that doctors are really experimenting every day. Every time a prescription for sulphonamides is written an experiment is started, and one not free from danger. An effort is being made to find out

whether the patient's illness will respond or not. The trouble is that most of the experiments are bad ones; they almost seem to be designed to perpetuate ignorance instead of to give the answer to a question. I would only ask that the experiments should be designed a little more logically to find the answers. This is the real essence of research, which, as I have said, is an attitude of mind. It is an attitude of mind which is not taken in by custom, prejudice, or false logic, but which seeks to find an answer. Those who are disinclined to depart from custom might remember that the man who first gave up the practice of blood-letting departed from the custom of his day. No one would doubt that he was a benefactor to mankind.

An example of a good therapeutic experiment came to my notice a little while ago. My friend Dr. Peter Duncan is interested in lymphocytic choriomeningitis. A case was admitted to hospital which he had reason to believe (and later proved) to be in the pre-meningitic stage of this disease. There is some doubt about whether it responds to aureomycin. Duncan thinks that it does not, and that others who claim benefit from its use have given aureomycin at the stage when the second (meningitic) temperature peak is about to run its natural course towards resolution. He therefore gave this man aureomycin in full doses in the pre-meningitic phase, and proved that, so far from having an effect, it was powerless to prevent the second rise of temperature and the onset of meningitic symptoms. Thus by giving an expensive drug which he believed to be useless, in such a way that its value, if any, could be assessed, he proved his point, and at the expense of a few pounds may have saved hundreds of other cases from being treated in the same useless manner. I know that one case is not proof, but in an experiment as well designed as this one it is very strong evidence. Moreover, choriomeningitis is a fairly uncommon disease, but I am sure that if practitioners cared to make a few properly recorded critical experiments of this kind they could be the means of putting to an end a great deal of useless, expensive, and misapplied therapeutic efforts.

Further Suggestions

But let us continue. Do constipated people really need aperients, or would they after a time develop a normal habit if given a placebo medicine? Is there any association between constipation and halitosis? Is emphysema a hereditary disease, or can it perhaps be divided into a group that is hereditary and another that has a known aetiology such as asthma or bronchiectasis? And, finally, does tooth-brushing prevent caries?

This is where we came in. These are only a few suggestions about problems which might be investigated in general practice; most of them, I submit, have both interest and practical importance. There must be hundreds of other problems, the best ones being those that one thinks out for oneself. Some of them come to mind by reflecting on one's experience; for instance, by getting a clinical impression that a certain complaint seems to be particularly common in workers at a certain trade, and collecting statistical information to find out if the impression is correct. Others will come as heaven-sent opportunities; for instance, you might discover by careful observation something about the epidemiology of Bornholm disease, or even poliomyelitis, or you might find a combination of two rare dominant genes, such as those of retinitis pigmentosa and von Recklinghausen's disease, occurring in one and the same family. Quite a small group of carefully compiled observations on the behaviour of these genes in three generations would suffice to show whether they were carried on the same chromosome pair (see Fraser Roberts, 1945), and thus assist in the mapping of the human chromosomes.

Conclusion

I have not consulted any literature on the suggestions I have made. The answers to some of the questions may be already known, but I doubt if they are. Any investigation

of these problems would have to be carefully thought out and a plan of campaign prepared. Literature might have to be consulted. Snags would be inevitable, and changes of plan would be required. Very few researches work out as one expects. Above all, one must be prepared for the results to be negative or to be the reverse of what one would like to prove. A willingness to admit defeat is part of the attitude of mind, and, as I said at the beginning, it is really only the attitude of mind which distinguishes the research worker from his fellows.

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IS EARLY TREATMENT ESSENTIAL IN CANCER?

BY

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In view of the many characteristics of cancer, the advice often given, that treatment should begin as soon as possible after symptoms are recognized, is almost taken for granted; but this point of view has recently been challenged in the *British Medical Journal* (1952). Over and over again in the valuable *Survey of Cancer in London* by W. L. Harnett (1952) we meet a concluding statement such as: "There is no significant difference between the survival rates of those who come under treatment within the first six months of noticing symptoms and those in whose cases the delay was longer." The treatment in question has for the most part been surgical or radiological. The author was careful to point out that this does not mean that there is no difference in the survival rates of patients when treated in the *early* or *late* stages of the disease. It is because there are often such significant differences that the urge for early treatment arises, but it does not follow that the duration of symptoms before treatment is necessarily brief in Stage I cases or long in the later stages.

Details of 695 Cases

I have been fortunate in gaining access to data relating to the radiation treatment of cancer of the cervix uteri in 695 cases the details of which were not given in the survey mentioned. In Table I the data show how the duration of symptoms before treatment is distributed for Stages I-IV of the disease.

TABLE I

Duration of Symptoms Before Treatment	Stage I	Stage II	Stage III	Stage IV
1-3 months ..	74	128	88	27
3-6 " ..	26	61	46	14
6-12 " ..	22	45	31	6
Over 12 " ..	13	31	26	11
Not known ..	14	22	9	1
Totals ..	149	287	200	59

Further data in Table II respecting these patients show how the numbers of five-year survivals are related both to the stage of the disease and to the duration of symptoms before treatment.

The whole of the subsequent argument here is based upon the validity of the data under the heading "Duration of symptoms before treatment"; this is a quantity which depends in no way upon medical observation, because it is what the patient thinks at the time the questions are put.