Collective Investigation

AN EXPERIMENT IN CARRYING OUT CONTROLLED THERAPEUTIC TRIALS IN GENERAL PRACTICE

W. N. LEAK, M.D.
Winsford

P. R. BATESON, M.B., B.S.
Research department, Mining and Chemical Products Limited

The experiment to be reported here was sponsored and organized by the Research Department of Mining & Chemical Products Limited. Its aim was twofold. First of all it was hoped to gain some idea of the effectiveness of certain drugs in general practice and it was also hoped that the experiment itself would throw some light on the planning and technique of such an investigation. Its object was to supplement rather than supplant data obtained in hospital practice. For many years pharmaceutical firms have sponsored university, hospital and laboratory research on new products. This was to be a tentative extension into the field of general practice.

Preliminary Considerations

There are, however, many difficulties involved in undertaking clinical trials in general practice. Doctors in this field are hard worked and have little time to plan research programmes for themselves. Furthermore, contact among general practitioners interested in similar research projects can be extremely difficult. The problem is being tackled by the College of General Practitioners, and the research project to be described was planned with its approval and assistance. Though the British Medical Association had no official connection with this project there did happen to be two members of the B.M.A. Council who took part in it, Dr W. N. Leak, who took the chair at all the conference meetings, and Dr J. I. Milne of Manchester, a doctor of rare charm and ability, who unhappily died before it was completed.

This paper sets out to give the problems to be faced, the way in which they were met, the cost in time and money, and it attempts to draw conclusions. It is concerned mainly with the organization of the project. A second paper giving the clinical results will be published by those taking part in the investigation when their observations have been completed and analysed.

In general practice certain points seemed essential in any pilot scheme. First of all it was necessary to choose a fairly common complaint which does not endanger life and in which it was legiti-

mate to use a medicament whose composition was unknown to the doctor conducting the treatment. A corollary of this was that the doctor could be assured that each of the medicaments supplied was believed to have some beneficial action in the condition under consideration.

Without this assurance it would be impossible for the doctor to give it to his patient with that confidence which is an essential part of the doctor-patient relationship in general practice. A double blind trial is quite impracticable. These are severe limitations, and it might be thought that nothing of a satisfactory nature would emerge as a result. We believe, however, that the experiment was well worth while and that a description of the trial and the way it evolved should be of general interest.

One condition which fulfilled the requirements is peptic ulcer. It is common, baffling, and there are medicinal agents in plenty. It is largely treated by general practitioners and the Company happens to be interested in discovering the method of action of various substances in its treatment. There is also no lack of academic literature and experience on the subject, so this was the subject chosen for this trial investigation—ambitious but full of scope.

Establishing a Research Group

The first difficulty was to find practitioners who might be interested in attempting such research, and the following figures are of interest.

In 1953 the Company circulated 8,000 practitioners asking them to take part in a preliminary investigation. This involved treating one case of peptic ulcer with a known medicament and sending in a clinical report a month later. 325 doctors (4 per cent) accepted the invitation, 300 cases were actually started and 110 final reports were received. This was rather disappointing, but at least 100 doctors were found who had a sustained interest in such projects, and there were 225 more who possibly might do such work. Other methods of approach and other topics might have shown a different proportion.

With these 100 doctors in mind a more serious investigation was envisaged, and it was decided to test the results in general practice of three antacids. The doctors were to be asked to include in the trial all peptic ulcers as proved by x-ray investigation. Each case was to be started on a course of a medicament, the nature of which was unknown to both doctor and patient but believed to be effective; the patient was to report for follow-up at 3 weeks, 6 weeks, 3 months, 6 months, 9 months and 1 year. At the end of this period a final assessment was to be made in which the patient's health in respect of ulcer during the year of the trial was to be compared with the

previous year. In order to collect this information, the recording system had to be simple.

Recording Results

The final details of the forms to be used were decided after consultation with the research committee of the Council of the College of General Practitioners.

Record Card No. 1 (figure 1) provided information concerning the patient's ulcer history, the severity of symptoms, and the nature of previous treatment. It also gave details of age, sex and occupation. Facilities for a carbon copy were included and the latter was returned to Dr Bateson; the original was to be kept by the doctor.

Record Card No. 2 (figure 2) was provided to report the result of the follow-up. Again carbon copying was used, and after each follow-up the appropriate strip was detached and returned.

A Final Assessment Form was used at the end of the trial.

In addition to these forms, each doctor was given a supply of reply paid envelopes, a supply of cards requesting further quantities of medicaments, and a supply of cards which could be sent to patients requesting them to attend the follow-up.

Progress of the Trial

All this took time, but towards the end of 1954, 90 doctors were asked to take part in the new investigation. The invitation was in the form of a letter, and included a summary of the proposed plan. Twenty-two doctors accepted the invitation, and the majority of these were visited in their home towns. The purpose of the visit was threefold; first, to make clear the details of recording; secondly, to assure the doctors of the sincerity of the project; thirdly, to make an assessment of the doctor's genuine interest in research of this kind.

Of the 22 doctors who accepted this invitation, 17 were visited in the first quarter of 1955. At the end of October 1957, 13 of the 17 visited were still taking part in the investigation, while only one of the five not visited was doing so, the other four falling out in the first six months. The reasons for the four who were visited dropping out were death, retirement, overwork, and in one case unknown.

The trial was started on June 1st, 1955, and at October 1st, 1957, it was decided to include no new cases. Before the trial started it was estimated from information provided by the participants that at the end of two years 210 cases would have been included: the actual number at October 1st, 1957, was 214. The number of cases discontinued was 28, most of which came from the doctors who have

Record Card No. 1. **PEPTIC ULCER TRIALS** GROUP 1/2/3

PATIENT'S IDENTIFICATION : Code letter..... Case number.....

Age..... Sex..... M/S/W/..... Occupation..... Children if any.....

ULCER HISTORY

Date of first dyspeptic symptoms.....

GU/DU.....

Date of last attack requiring treatment by doctor.....

Approximate duration of longest attack.....

Approximate duration of longest period of freedom.....

Approximate time off work in past 12 months.....

Most prominent symptoms during attack:—

Epigastric pain..... Flatulence .....

Vomiting..... Heartburn .....

Treatment employed in previous attacks:—

None.....self-medication.....

Treatment by doctor

Bed ..... Medicaments .....

Ambulant ....

Diet..... .....

PRESENT ATTACK

Date of onset.....

Date of first medical advice.....

Most prominent symptoms:—

Epigastric pain ..... Flatulence .....

Vomiting ..... Heartburn .....

Severity .....

Date therapy commenced.....

Group 1 2 3.

Most recent x-ray dated .....

Findings .....

FIG. 1.

withdrawn. The effective number of cases in the trial was 186 and the distribution was:

On antacid 1	67
On antacid 2	61
On antacid 3	58

At December 31st, 1957, the theoretical number of cases which should have been followed up completely for one year was 164; the actual number was 145, a deficit of 11.5 per cent.

We expect at least a further three of these cases to be completed in due course. The total number of follow-up reports due in respect of all cases in the trial was 1,081; the number received was 1,036, a deficit of 4.1 per cent. If cases started by doctors who eventually withdrew from the trial are left out the deficit in follow-ups is less than 2 per cent. This is a remarkably low figure, and as only three cases were lost through removal from their areas it suggests that in spite of the frequent changes in population in some areas long term projects are quite possible.

Conferences

It was decided at the start of the trial that a useful purpose would be served by providing the participants with an opportunity to meet and discuss the trial at fairly regular intervals. It was also decided that at such meetings it would be a good plan to invite officially some members of the research committee of the council of the College of General Practitioners, and also guests who had made a study of various aspects of peptic ulcer. Three such meetings were held between May 1956 and October 1957 at Harrogate, Eastbourne and Marlow. At the second and third conferences participants were invited to bring their wives. These conferences have been of great value in enabling the participants who came from all parts of the country to meet and discuss matters of common interest. Personal contacts and the conferences have overcome any apprehension or suspicion of the sponsors' intentions: it is significant that few of the doctors who were visited have failed to sustain interest.

At the last conference, it was clear that all those participating enjoyed taking part in this project. They did not find that the work involved was very great. They did not think that it in any way affected their doctor-patient relationship. In fact, they felt that they were becoming better equipped to manage their ulcer cases. They were pleased to have the opportunity of discussing common problems with fellow general practitioners. They were all anxious to carry on with projects of this nature, and willing to introduce new members to the group. This is the desirable method of expanding a research group of this nature. It obviates any need on the sponsors' part for

Record Card No. 2 - Follow-up. **Group 1/2/3**

PEPTIC ULCER TRIALS **Group 1/2/3**

	weeks 3	*weeks* 6	*months* 3	*months* 6	*months* 9	*year* 1
Patient's identification — Group .. Code letter Case No...						
Response:						
1. Complete	1	1	1	1	1	1
2. Partial	2	2	2	2	2	2
3. No relief	3	3	3	3	3	3
If relief not complete persistent symptoms:						
1. Epigastric pain.. ..	1	1	1	1	1	1
2. Flatulence	2	2	2	2	2	2
3. Heartburn	3	3	3	3	3	3
4. Vomiting	4	4	4	4	4	4
X-ray control:						
1. Ulcer healed	1			1		1
2. Ulcer smaller	2			2		2
3. No change	3			3		3
4. Ulcer larger	4			4		4
Relapse:						
1. Yes	1	1	1	1	1	1
2. No	2	2	2	2	2	2
Further treatment if any:						
1. No	1	1	1	1	1	1
2. Yes	2	2	2	2	2	2
Patient's views on therapy:						
1. Good	1	1	1	1	1	1
2. Indifferent	2	2	2	2	2	2
3. Poor	3	3	3	3	3	3

Please tick applicable numbers and then detach appropriate section and return to M. & C.P.

This sheet to be retained by the doctor who may wish to complete the following for his personal records:—

Patient's Name

Address

File reference

FIG. 2.

explanation of their purpose or proof of their integrity. It should make possible new investigations at a faster rate on a broader front.

Administration

The administrative task has been considerable. Over the course of 2½ years, the file of each participant contains between 60 and 70 letters. It has been necessary to keep a careful check on the dates upon which follow-up reports were due, and we have kept the doctors informed of which patients should be seen each month. It is clearly essential in work of this nature that the administration should be efficient. Lack of interest by the co-ordinators must of necessity be reflected in the work of the participants.

It was originally planned that each case should have x-ray control at regular intervals. Those doctors visited said that facilities for such examination were readily available; nevertheless, events have shown that less than 5 per cent of cases have been subject to radiological control. The reasons for this will be given in the clinical report. It became clear that in assessing the therapeutic results of this investigation clinical results would have to be used exclusively, so plans for the trial had to be altered; this emphasizes that any administration must be flexible, and preconceived ideas may need modification.

Discussion and Conclusions

Over the past ten years a considerable amount of research has been carried out in general practice, but the doctors undertaking this have been restricted in numbers or resources. It has been suggested that there is only a limited number of general practitioners prepared to do such work, and that saturation point may soon be reached. Prior to this investigation, many of the doctors taking part had not previously been engaged in research work. This pilot survey suggests that there may be a fairly large number of doctors who, if stimulated, would be anxious and willing to engage in original work in their practice if suitably organized and financed.

This investigation has shown that it is possible to correlate the efforts of widely distributed practitioners, and to carry out a controlled therapeutic trial in general practice. Our experience shows the great importance of adopting the correct sequence of procedure.

1. Establish a group of doctors interested in a broadly defined research project.
2. Establish personal contact with participants.
3. Prepare a detailed plan of the project taking into account information gained during visits. The task of the doctors in the trial must be simple yet interesting.
4. Provide opportunities for the participants to meet.

It has become clear that such a project, if properly handled,

can be sponsored by the research departments of pharmaceutical companies. The cost of this trial was approximately as follows:

	£
Cost of medicaments	400
Cost of report cards, etc.	150
Postage	150
Meetings and personal visits, etc.	700
Time and labour of staff	700
	£2,100

This works out at £10 per patient in the trial. Consideration of the methods used in relation to the results obtained suggests that such a cost is by no means excessive. It would seem that industry is well placed to undertake research expenditure of this magnitude. If it does not, much essential work will go undone or be long delayed. If Mining & Chemical Products Limited gain from this trial some indication of the relative therapeutic value of the three medicaments tested it will, from their point of view, have been worthwhile. At the same time, experience in taking part in a controlled research project is of value to the general practitioners taking part, and also, without additional cost or burden, it has been possible to gain valuable information about general practice and about peptic ulcer as it presents in that sphere of medicine. If this method of investigation can be extended to other conditions, it may lead perhaps to a better understanding of those conditions and more successful therapy. In time it ought to bring a closer approximation in methods and outlook between those engaged predominantly in hospital and general practice.

ACKNOWLEDGEMENT

General practitioners taking part in this trial were:

Dr H. G. Barnes, M.B., B.S.
Dr L. R. Holt, M.A., M.B., B.CH.
Dr N. Lawrence, M.R.C.S., L.R.C.P.
Dr A. J. Levine, M.B., CH.B.
Mr C. Noon, O.B.E., F.R.C.S.
Dr R. A. O'Shea, M.B., B.CH., C.P.H., D.OBST.R.C.O.G.
Dr S. S. Rowell, M.R.C.S., L.R.C.P.
Dr E. Sklar, M.R.C.S., L.R.C.P.
Dr H. Sless, M.B., B.CH.
Dr T. E. S. Stowell, B.M., B.CH.
Dr M. G. Stratford, M.R.C.S., L.R.C.P.
Dr B. M. Toop, M.R.C.S., L.R.C.P.
Dr D. Vining, M.B., CH.B.
Dr J. T. Woodhead, M.A., M.R.C.S., L.R.C.P.
Dr J. I. Milne, M.B., CH.B. (deceased)

The success of the project is entirely due to their co-operation and the results of the therapeutic trial will be published under their names. We also wish to thank the following for their help and advice: The research committee of the College of General Practitioners, and the following guests who attended the conferences—Dr John Fry, Dr Thomas Hunt, Dr R. F. L. Logan, Dr W. J. H. Lord, Dr C. Naish, Dr C. N. Pulvertaft, Dr G. I. Watson and Professor Soehring of Hamburg.