British experience of the pill *

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OF all the problems of the next decade none is of greater importance than population control. It has taken half-a-million years to produce the present world population of 3,000 million, but unless growth is checked this number will be doubled in only 35 years' time. In 1964 the American Medical Association[1] adopted this statement as official policy; 'An intelligent recognition of the problems that relate to human reproduction, including the need for population control, is more than a matter of responsible parenthood; it is a matter of responsible medical practice.'

How far is the oral contraceptive meeting this staggering challenge of the population explosion? At the present time the Pill is used by 18.5 million women throughout the world,[2] but there are 700 million women[3] who could use the method but do not do so. The reasons for this are many and varied, but prominent among them is the fear, which may well be unjustified, that the Pill is unsafe. There are too many suspicions and too few facts for the medical profession to be able to offer accurate advice to a prospective user or to any responsible government agency.

Need for further research

What are the disadvantages of the oral contraceptives and how far are these offset by their high efficiency and their other beneficial influences on health? At the moment we do not have a complete answer to this question. It was clear that if we were to try to find an answer, to try to draw up a comprehensive balance sheet of good and bad, a very large-scale study of total reported morbidity was required and that such a study must make provision for the observation at the same time of a comparable control population of women who had never taken the Pill.

The Royal College of General Practitioners believed that a special opportunity, and indeed a special responsibility, existed for carrying out such a study in general practice in the United Kingdom. First, under the British National Health Service patients have to register with a doctor of their choice. This means that the general practitioner has a record for each of his patients whether or not they have consulted him. In epidemiological terms, the doctor holds information on the total population for which he is at risk. It is possible to make a random selection from this known population in order to obtain a representative control series. Without this fortuitous facility the study would not have been possible. Secondly, it has long been the custom in the United Kingdom for specialists to see patients only if they have been referred by their general practitioner. The specialist reports his findings and opinions back to the family doctor. As a result of this practice, which is rarely neglected, the general practitioner becomes aware of almost all morbidity of which the patient complains. Finally, the College had had a considerable amount of experience in the organization of multi-observer research projects in general practice. This gave it confidence that a study on the scale envisaged could be achieved.

*Based on a paper given at the joint meeting of The College of Family Physicians of Canada and The Royal College of General Practitioners held in Toronto on 29 September to 2 October 1969.

Designing the study

Planning began in January 1966 with the appointment of a Working Party. We realized from the start that in order to bring under observation a sufficiently large number of patients it would be necessary to call upon the help of many general practitioners who had never previously undertaken any research. So it was important to devise a simple routine for the random recruitment of both the oral contraceptive users (the takers) and the controls. This proved to be a fairly easy task and the method chosen, which I will explain in detail later, was tested in a small pilot trial started in October 1966, and in a modified form it was further tested in a second trial using 90 doctors in October 1967.

A much more difficult task was to find a solution to three closely inter-dependent problems. Firstly—How many patients were required to ensure a statistically-valid result? Secondly—What was a reasonable number of patients for each doctor to recruit and observe? Thirdly—How many doctors would volunteer to take part in the study? None of these factors could be accurately predicted. Logically, we should have started with the first and the remainder should have followed, but we knew that the limiting factor would be the number of practitioners who would volunteer to take part. We decided that the study should continue for five years and so, with the experience of the pilot trials to guide us, we took an inspired guess and decided our minimum requirements (table I).

TABLE I
MINIMUM REQUIREMENTS FOR THE STUDY

1,000	doctors
20,000	takers
20,000	controls

The purpose of the project was not only to study the suspected relationship of certain illnesses to the taking of oral contraceptives, but also to attempt to reveal if there existed any relationships of which we had no previous suspicions. We were not setting up a study to test a closely-defined hypothesis. We were certainly not going to conduct a drug trial. Our aim was the much broader one of studying the natural history of two large comparable groups of women. One of these groups consisted of women who had chosen the Pill as a method of contraception, while the other group had not done so, but it was impossible to calculate whether our target of 20,000 takers and a similar number of controls, observed for five years, was adequate to achieve such an ill-defined objective.

Nevertheless, we had to be sure that we should not be embarking upon a study that was doomed from the outset for lack of numbers, nor one that was grossly extravagant. We therefore chose a few conditions which it was thought might be adversely affected by the Pill. Starting with the known incidence of these in the community, we calculated the number of takers it would be necessary to observe to demonstrate an arbitrary doubling of incidence at the commonly accepted five per cent level of statistical significance (table II). These calculations gave us some confidence that our plans were of the right order of magnitude.

TABLE II
OBSERVATION OF TAKERS REQUIRED FOR SIGNIFICANT FINDINGS*

Diabetes	8,000	women/years
Liver disease	11,000	,, ,,
Myocardial infarction	57,500	,, ,,
Pulmonary embolism	125,000	,, ,,

*For explanation see text.

These were the basic logistics of our plan. They meant that each participating doctor would be asked to recruit two takers and two controls each calendar month for about a year. This work-load was one of the factors tested in the second pilot trial and was found to be acceptable.

At this stage three major doubts remained to be resolved. Firstly—Could the minimum of a thousand general practitioners be persuaded to take part? Secondly—even assuming that such a number could be achieved, could they be moulded into an effective epidemiological research team? And thirdly—Who was going to find the large sum of money necessary to finance the study? An application for a grant was made to the British Medical Research Council. Following the presentation of the results of the second pilot trial, in a remarkable and praiseworthy act of faith, the Council agreed in February 1968 to finance the study, subject to a report of satisfactory progress after 18 months. The most significant single indication of our success so far is that this condition was withdrawn after only ten months.

Progress

How, then, has our progress compared with our aim? The main study started on 1 May 1968. At the present time, 1,400 doctors are participating. Recruitment ended on 31 July 1969 when 45,000 women had been placed under observation, which will continue at least until 1973. An office has been set up in Manchester with a full-time staff of ten. This office is responsible for the co-ordination of the study and for all data processing. The study is conducted in close association with the Manchester University department of social and preventive medicine, and with the department of computation in the university's Institute of Science and Technology.

In a study of this size it was, of course, essential to use the computer for data storage and analysis, but we have also devised methods which I shall describe shortly for using the computer as an important element in the administration.

Recruitment of subjects

I should now like to explain the methods used to ensure that the family doctor recruited representative samples of both takers and controls by a random method. Each doctor was instructed to recruit as takers the first two patients in each calendar month for whom he wrote a prescription for an oral contraceptive. This could be the patient's first ever such prescription, or it might be a repeat. The patient had to be interviewed by the doctor so that he could complete with accuracy the registration document. These documents were stamped before issue in each section with a unique serial number and also with the doctor's name and address. At the start of the interview the doctor writes the patient's name and address on the index slip at the top of the card. The remainder of the information obtained at the recruitment interview is recorded on both sides of the centre section of the record. We call this part the recruitment card. Here are recorded details of the patient's history and personal status. No examination is required. We have stipulated that all subjects recruited, both takers and controls, must be married or living as married. When the recruitment card has been completed, and the interview takes no more than five minutes, the registration document is divided. The recruitment card is immediately posted to the central office. The right-hand section is folded and inserted into the patient's medical record envelope and on this card the doctor records details of the first six months of prospective observation of the patient. The left-hand section is what we call the tracer card. This is also inserted into the patient's medical record envelope, where it shows up as a marker. If the patient should ever change her doctor this tracer card is automatically transferred with her medical record to her new doctor and it bears a message inviting him to continue the observation of this patient. Finally, at the end of the interview, the index slip is attached to the index sheet. This is the only cross reference that exists between the patient's name and the study serial number, and it is known only to her own family doctor. Thus, complete confidentiality is ensured.

The next step is to select a control patient for this taker. Starting with the taker's

record in the doctor's file, each subsequent record is examined in alphabetical order until the next record of a woman whose year of birth is within three years either side of that of the taker is found. Like the taker, she must be married or known to be living as married. The record then must be examined to see if the Pill has ever been prescribed for her. If it has, then she cannot be recruited as a control and the file search continues. When an apparently eligible control patient is found she must be contacted in order to arrange an interview with her. The first objective of the interview is to obtain the patient's confirmation that she has never taken an oral contraceptive at any time for any purpose. Her medical record alone may not be completely reliable on this point. If the prospective control patient has taken the Pill at any time, then she cannot be recruited as a control subject and the file must be searched further for an acceptable control. If all is well, however, and the patient has never taken the Pill, the interview proceeds in the same way as for a taker. At the end of the interview the control's index slip is also attached to the index sheet.

The doctor records the diagnosis of all episodes of illness newly presenting after the date of recruitment on the observation record. This also has space for the recording of oral contraceptive prescriptions given to the takers, and for information about certain special conditions, including pregnancy and death. If a control subject starts to take the Pill, the information is simply noted in the prescription section of the record and her observation continues. However, the doctor is asked to recruit a new control to replace the one who has become a taker. Each observation record is recalled by the central office after it has been in use for six months and it is replaced by a new record.

Central organization

At the central office in Manchester, records arrive at the rate of 2,000 each week. After sorting and counting they are taken for coding. Four of the staff are employed full-time on this task. They use the *International Classification of Diseases* for coding morbidity and deaths, and the British Registrar General's *Classification of Occupations* (1966) for coding social status. During the coding, each record is carefully scrutinized, and if the coders find any omissions, errors, ambiguities or inconsistencies, a photocopy of the record is made, and it is returned to the general practitioner with a politely-worded letter asking for clarification. We have found that approximately 15 per cent of all records have to be dealt with in this way, but eventually all are returned to us properly completed. We have come to realize that this process of referring back records for the up-grading of data is an essential feature of a multi-observer study and it is one of the ways in which we have been able to convert 1,400 self-confessed individualists into an effective research team.

After the records have been carefully coded they are all independently checked before they are stamped 'coded' and passed for punching on to paper tape. The punching is again double checked, each batch of records being punched by two different operators, each correcting the work of the other. Finally, the verified paper tapes are input to the computer, during which a comprehensive series of tests are applied and any remaining error is identified and the inaccurate record rejected. And so the coders check the doctors' records, the coders' own work is independently checked, the punching is double checked, and the computer finally checks the whole process. Only in this way can accurate information be assured. No amount of sophisticated computer manipulation can turn bad data into good research.

I mentioned earlier that the computer is used as an essential element in the administration of the study. The date of recruitment of each patient is stored in the computer and every six months from that date the computer prints out a new follow-up record for that patient. These records are received at the central office in batches of 1,000–2,000 joined together end-to-end and with sprocket holes down each side. A machine

is used to trim the sides of the continuous stationery and cut it into individual records. These follow-up observation records are then placed on another machine which folds them twice and places each one into a window envelope so that the address is visible. The envelopes then pass through an automatic postal franking machine which also seals them and they are then ready for collection by the postman.

The receipt by the doctor of a follow-up record is accompanied by a request for the return of the previous record. If, after a month, this has not been received by the central office and input to the computer, the computer prints out a reminder letter which is then posted to the doctor. If this also fails to produce any reaction, a month later, the computer prints a list of the missing records and we write a personal letter to the doctor.

Communications

The Royal College of General Practitioners has 24 regional faculties. When we reached the stage of the second pilot trial we invited each of the faculty research committees to nominate four doctors to take part. At a later stage the faculty research committees nominated one of these four participants to take special responsibility for the study within his faculty. We have called the 24 regional representatives faculty co-ordinators. All of them had had experience in the pilot trial, and since then we have called them together for special briefing meetings both immediately prior to the launching of the main study, and at intervals since. They in their turn have organized meetings within their own faculties for the local participants, and these meetings have been addressed by me or another member of the working party. A tape recording and a set of 34 colour slides about the study were made available for borrowing by any participant. These were sometimes used at faculty meetings, or at more informal meetings of small numbers of participants in their own homes.

The names and telephone numbers of the faculty co-ordinators were made known to all the participants, who were encouraged to contact them if they so wished when they had any problems with the study. Naturally, a large number of participants address their enquiries to me at the central office and a large correspondence has accumulated. Whenever any points of importance arise in my reply a copy is always sent to all the faculty co-ordinators. In this way they are kept up to date with developments. However, it was felt that closer personal contact between the central office and each participant was desirable and so we have started to send out news sheets. In this way we have been able to reiterate points which were causing difficulty, introduce new instructions, and most important of all, provide a feed-back to the doctors of analyses of the data they have collected.

Early results

The study is still in its early days and so far we have not been able to produce any analyses of the morbidity that is being observed. We have, however, obtained some simple analyses of some of the parameters recorded on the recruitment card. These analyses were made in June 1969 before the recruitment phase had ended. Because controls are necessarily recruited after their respective takers there was bound to be a shortage of controls at this stage and this is illustrated in the analyses of the age distribution of the takers and controls (table III).

There was a particular shortage of the youngest controls and this confirmed the difficulties that many participants had expressed in finding young women who are married and yet have never taken the Pill.

Table IV shows the social status analysis and indicates that there are fewer women in the lower social groups on the Pill than in the control series. Seventeen per cent of

the takers are in social classes IV and V, as against 20 per cent in the controls. Although the difference is small it is highly significant statistically.

TABLE III

Age	Takers		Controls	
	No.	Percentage	No.	Percentage
Under 15	0	0	0	0
15–19	806	5	376	2
20–24	5,039	29	4,104	27
25–29	4,629	26	4,319	28
30–34	3,623	21	3,362	22
35–39	2,263	13	2,009	13
40–44	996	6	986	6
45 and above	260	1	281	2
Not known	0	0	0	0
	17,616	100	15,437	100

(chi squared = 22.5, p. <.001)

TABLE IV

Class	Takers		Controls	
	No.	Percentage	No.	Percentage
Not known	68	0	56	0
I	1,237	7	1,012	7
II	3,188	18	2,690	17
III (non-manual)	1,963	11	1,884	12
III (manual)	7,428	42	6,515	42
IV	2,170	12	2,107	14
V	867	5	871	6
Students	188	1	74	0
Officers	95	1	35	0
Other ranks	412	2	193	1
	17,616	100	15,437	100

(chi squared = 27.9, p. <.001)

TABLE V

No. of births	Takers		Controls	
	No.	Percentage	No.	Percentage
0	2,571	15	3,172	21
1	3,439	20	4,312	28
2	5,697	32	4,785	31
3	3,490	20	1,989	13
4	1,437	8	693	4
5 and above	967	5	480	3
Not known	15	0	6	0
	17,616	100	15,437	100

(chi squared = 22.5, p. <.001)

TABLE VI

NO OF CIGARETTES SMOKED/DAY

No/Day	Takers		Controls	
	No.	Percentage	No.	Percentage
0	8,848	52	8,742	58
1– 4	1,089	6	891	6
5– 9	1,298	8	1,046	7
10–14	2,337	14	1,918	13
15–19	1,500	9	1,109	7
20 and above	2,005	12	1,234	8
	17,077	100	14,940	100

(chi squared = 189, p. <.001)

With parity (table V) the differences are greater. Thirty-three per cent of the takers have had three or more children against 20 per cent of the controls. Thus it appears that the Pill is still being used to a great extent in Britain for family limitation rather than family spacing, although I think this tendency is now changing.

The importance of these analyses is not that they show anything new. On the contrary, their value is that the distributions are exactly what we expected. This strongly supports the view that patients are being properly recruited by their doctors, that they are representative of their respective populations in Britain, and the validity of the whole study depends upon this.

One analysis, however, has revealed new and important information (table VI).

Women on the Pill are more likely to smoke cigarettes and smoke heavily than the controls.[4] The average daily cigarette consumption is 20 per cent higher in the takers than in the controls, and this difference is statistically highly significant. We are satisfied that this observation is representative of the population of the United Kingdom but we cannot say whether the same is true of other countries or cultures. We have not been

able to find any published evidence that smoking is associated with an increased risk of venous thrombo-embolism, but it is not possible at this stage to exclude this entirely. Nevertheless, it is now clear that no observed morbidity or mortality can be unreservedly attributed to the effect of the Pill unless the possible influence of smoking habits has first been excluded.

Conclusion

And so, we now feel confident that we have set up a study that can make a contribution to our knowledge of the effect of the present oral contraceptive agents. We may also learn something about the characteristics of women who choose the pill and about those who reject it. Perhaps our results will provide a more secure base from which research for a better product can begin. It may be that we have demonstrated something of greater importance—that meaningful large-scale morbidity statistics can be accurately collected from the point at which the greatest information is available—the records of the family physician.

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The hospital apprentice

The apprenticeship system, in medical teaching, which existed in the Minto House Hospital days, and which came to a close soon after 1837, had great advantages when under masters who held office in an hospital, dispensary, or any large institution, and when studies and habits were properly supervised; but under other circumstances that bond was a waste of time, and the result in many instances unfavourable, even disastrous. In the early course of the student's life, under such masters as Abercrombie, the Bells, Liston, Lizars, Syme, and others, there was less theoretical teaching, less done by cramming and more by private practical instruction and impressions photographed, as it were, on the brain from sight and touch. The study was thus made fascinating from its commencement by the gradual child-like opening up of a road through the gates of the senses to higher knowledge; and so by quickening the power of observation, desire was created for further insight of the mysteries of life, health, and disease. The tendency of this on passing the successive mile stones of study was to intensify interest in the wonderful developments and adaptations both of the science and art of medicine; and thus it was in those early days at Minto House.

Recollections of Dr John Brown with a selection from his correspondence. Alexander Peddie, M.D., F.R.C.P., F.R.S.E. Edinburgh and London. Oliphant, Anderson and Ferrier. 1894. Pp. 187.