The happiness pill?

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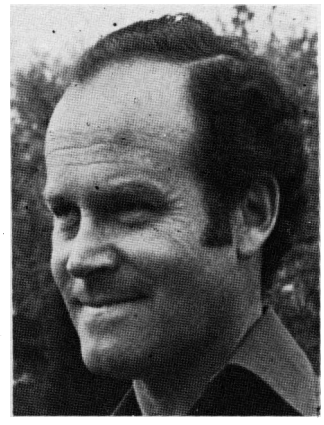

OVER the past 20 to 30 years, we have seen the introduction of a new application of the use of drugs. Women have been encouraged to take hormones continuously over many years, not as a cure for a disease, but as a means of prevention. During the reproductive years, the hormonal contraceptives have proved to be the most convenient and effective way ever devised of preventing unwanted pregnancy, and after normal menstruation has ceased, oestrogens have been recommended to prevent the effects of declining natural function of the ovaries.

When post-menopausal hormone therapy began to be promoted by the popular press in Britain, the tablets were called 'the happiness pill'. I do not need to stretch literary licence very far to include oral contraceptives in the same term, for they have played a major part in promoting a new degree of freedom, equality, and, I hope, happiness for millions of women throughout the world.

No scientist has ever believed that such advantages could be gained without some degree of risk, but until fairly recently the price that had to be paid seemed to be small, and the value great. The use of the hormones expanded dramatically, and in 1977 over 80 million women throughout the world were taking oral contraceptives—an almost incredible degree of mass medication. But now doubts are creeping in and the use of hormones is declining. It seems an appropriate time, therefore, 20 years after the introduction of oral contraceptives, to review the history of this medicosocial revolution, and to trace its course, since our College has had an important influence on its progress.

Synthetic progesterone

Before the second world war, several workers had shown that oestrogens, or progesterone, when injected into a rabbit could inhibit ovulation (Makepeace *et al.*, 1937; Sturgis and Albright, 1940). Research was seriously hampered, however, by the enormous cost and scarcity of these hormones, which could be derived only from animal sources. To obtain 25 milligrams of pure oestradiol required four tons of sows' ovaries. A cheap source of synthetic hormones was required before any progress could be made.

Russell Marker was an organic chemist. A man of eccentric personality, he had no patience with administrative routine, and several times walked out of highly responsible posts without bothering about such trivialities as giving notice. In 1939 he was a professor in the State College of Pennsylvania, and that year managed to synthesize small quantities of progesterone from extracts of the root of the sarsaparilla plant. The yield was low, however, so he begged botanists to send him plants from all over the world. Soon his laboratory was filled with decaying vegetation.

In 1940, he found that the root of a species of yam growing wild in Mexico gave him a good yield. He immediately attempted to get financial backing for manufacturing in Mexico, but the whole world was now in conflict, and Mexico was not the most eligible of countries for developing new industry. He rapidly lost patience with cautious financiers, threw up his post in Pennsylvania, and bought himself a house in Mexico City. Using mules for transport, he explored the wilds of Mexico for the plants he needed. He set up a makeshift laboratory in the stables of his house and, working almost single-handed, began the synthesis of progesterone from a substance called diosgenin extracted from the root of a wild vine, a member of the *Dioscorea* species.

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Two European refugees, Dr Somlo from Hungary and Dr Lehman from Germany, had set up in Mexico City a small pharmaceutical business, which they called Laboratorios Hormona. One day in 1943, Marker walked into their building carrying two pickle jars wrapped in newspaper. The jars contained four and a half pounds of pure progesterone, worth well over a million dollars at present prices. The three men agreed to set up a new company to manufacture the hormone. It was incorporated in Mexico City on 21 January 1944. They called the company Syntex.

Satisfactory progress did not continue for long. Predictably, Marker had a disagreement with Somlo and Lehman and he left the company abruptly in 1945, taking his process notes with him. Production of progesterone ceased, and Marker virtually disappeared for over 20 years.

Syntex were now in serious trouble, but Dr Somlo found a 29-year-old fellow Hungarian who had taken his doctorate in Switzerland and was then working in Havana. George Rosenkranz, who is now President of the parent Syntex company, moved to Mexico City and rapidly re-established Marker's process. At many points he had to apply new chemical reactions to substitute for the steps recorded only in the notes Marker had taken with him. Soon, Syntex were supplying progesterone in bulk to pharmaceutical companies in the United States and Europe.

Orally active progestogens

The production of synthetic progesterone was a major advance, but like natural progesterone it had the disadvantage of having very low activity when given by mouth. Hormones were now being used for the treatment of gynaecological disorders and for threatened abortion, but they usually had to be given by injection. An orally active preparation was badly needed.

In 1949, a new chemist joined the Syntex company. Karl Djerassi was 25 years old. Born in Vienna, he was a naturalized American citizen and was trained in the University of Wisconsin. His Professor there, Dr A. L. Wilds, had been developing the observations of Ehrenstein at the University of Pennsylvania, and Birch in England, that if carbon atom number 19 was removed from the progesterone molecule, the new substance behaved biologically as a progestogen, but the activity (that is the potency) was different from that of progesterone (Allen and Ehrenstein, 1944; Birch and Mukherji, 1949; Wilds and Nelson, 1953).

Djerassi, working with Rosenkranz, methodically set about the task of removing the carbon 19 atom from the molecule of all the known synthetic progestogens. One of them, called ethisterone, had been synthesized by the Schering company in Berlin, as far back as 1938. In 1951, the Syntex team produced a compound that was identical to ethisterone, except that it was *without* the number 19 carbon atom. It was, therefore, called 19-*nor*ethisterone, and this proved to be a highly active progestogen when taken by mouth. It was not produced from ethisterone, however. Djerassi and Rosenkranz synthesized it in several stages, starting with the vegetable product diosgenin that Russell Marker had used. 19-norethisterone became known simply as norethisterone everywhere except the USA, where the name was later changed to norethindrone.

Biological and chemical testing of the new compound took several years. In 1954, Dr Roy Hertz (Hertz *et al.*, 1954) was one of the first to put it to clinical use at the National Institutes of Health at Bethesda, near Washington. He used it for the treatment of menstrual disorders.

The idea of an oral contraceptive

The compound was also sent for biological testing to Shrewsbury, Massachussetts—where there was a private research laboratory called the Worcester Foundation for Experimental Biology.

The director of this foundation was a biologist called Dr Gregory Goodman Pincus. Pincus had no doubts about the use to which he wished to put the new progestogen. He had always been interested in the problems of fertilization in animals. In 1951, the year that norethisterone was synthesized, a meeting was arranged between Pincus and two remarkable ladies, Mrs Katharine McCormick and Mrs Margaret Sanger.

Mrs Sanger was the doyen of the US birth control movement. A formidable lady, who suffered repeated vilification and even imprisonment for championing her cause, she combined many of the characteristics of Mrs Pankhurst and Dr Marie Stopes.

The connection between the International Harvester Company and oral contraceptives is not immediately apparent. In fact, the one had an important influence on the other (Reed, 1978). The Company was founded by Cyrus McCormick, whose son, Stanley, married Katharine in 1904. Two years later, Stanley developed severe schizophrenia from which he never recovered, although he lived until 1947. After a battle in the courts with her father-in-law, Katharine obtained control of her husband's fabulous wealth derived from the International Harvester Company, and devoted the rest of her life to supporting the suffragette and birth control movement in the USA. In this way she became a close friend and financial supporter of Margaret Sanger. In 1950, Katharine wrote to Mrs Sanger to ask her opinion about the priorities for birth control. Margaret Sanger replied: "I consider that the world and almost our civilization for the next 25 years is going to depend upon a simple, cheap, safe contraceptive to be used in poverty-stricken slums, jungles, and amongst the most ignorant people." It is one of the many ironies in the story of the Pill that when the miraculous product for which Mrs Sanger had prayed became available, it was used predominantly by educated women in the western

world, and to this day has barely penetrated to the "stricken slums".

Pincus was clearly impressed by Mrs Sanger's zeal, and even more by the offer of unlimited funds from Mrs McCormick. All the early development work on the Pill which Pincus now began was financed by Mrs McCormick, although the money was administered by the Planned Parenthood Federation in New York, an organization formed by Mrs Sanger.

The actual laboratory testing was carried out by Pincus's Chinese colleague, Dr Chang. It had been shown in 1937 (Makepeace *et al.*, 1937) that injections of progesterone would inhibit ovulation in rabbits. Oestrogens were also known to inhibit ovulation (Sturgis and Albright, 1940), but Pincus thought that they might be too risky, so Chang methodically tested progesterone injections, first in rabbits, then in rats, and was able to confirm that progesterone was an efficient ovulation inhibitor.

'Rebound' fertility

While this work continued in the laboratories of the Worcester Foundation, not far away, in Boston, Dr John Rock, Professor of Gynaecology at Harvard University, was administering oestrogen and progesterone to women. Far from testing their contraceptive effect, he was using the hormones for the treatment of infertility.

Rock was puzzled when a group of his patients failed to conceive even though it had been demonstrated that they were ovulating regularly. Because large quantities of oestrogens and progesterone are released in pregnancy, Rock argued that these women might be failing to conceive because they were short of these hormones, and that if they were administered they might induce a state of pseudopregnancy and stimulate development of the uterus and fallopian tubes. He gave continuous treatment to 80 women for three months. After the treatment was stopped, 13 of them conceived. This result was attributed to rebound fertility, and for many years the Pill was, wrongly, thought to have the same effect.

The disadvantage of the treatment was that the women suffered many of the unpleasant effects of pregnancy, including nausea, breast tenderness, and missed menstrual periods. Because progesterone has low activity by mouth, he was giving enormous doses—up to 400 milligrams daily.

By chance, Rock met Pincus at a scientific conference, and they discussed their mutual interest in hormones. Pincus suggested that progesterone might work on its own. He also proposed that the women should take the hormone for only 20 days, then stop to allow menstruation to occur, starting again on the fifth day of their period.

Thirty infertile women were tested by several methods, and shown to be ovulating regularly. They were all given the cyclic progesterone schedule. Most, but not all, failed to ovulate during treatment. However, when the treatment was stopped, they all promptly ovulated again, and shortly afterwards four of them conceived.

Rock was pleased with the result, but for Pincus the outcome was not so encouraging. Ovulation inhibition was not 100 per cent, and breakthrough bleeding occurred in some of the women. This was in spite of the massive dose of progesterone.

Use of synthetic progestogens

It was now obvious that it was worth trying the effect of a potent synthetic progestogen. Pincus had tested about 15 such compounds, but only two were sufficiently active by mouth (Pincus *et al.*, 1956). One was norethisterone which had been provided by Syntex. The other came not from Mexico, but from Chicago. Chemists at the laboratories of G. D. Searle and Company had been working, without publicity, for several years, and in 1954 Dr Frank Colton patented a synthetic progestogen, which was called norethynodrel. The similarity between norethynodrel and norethisterone was astonishing. The only difference was in the position of one double bond between two of the carbon atoms. In spite of the molecular similarity, there is no question that one was a copy of the other. They were synthesized by different methods and, indeed, had slightly different biological properties.

Progestogens as contraceptives

Rock tested both these progestogens in women who had been shown to be ovulating regularly. During progestogen treatment, given in the same cyclical pattern as the previous progesterone therapy, none of the women ovulated (Rock *et al.*, 1956).

In October 1955, the International Planned Parenthood Federation held a conference in Tokyo. With many misgivings, Pincus decided to present his results there (Pincus, 1955). He concluded his paper with the following cautious remarks:

"Much more investigation is, of course, needed, but they are thus far the most promising agents" . . . "We cannot, on the basis of the observations thus far, designate the ideal anti-fertility agent, nor the ideal mode of administration, but a foundation has been laid for the useful exploitation of the problem on an objective basis." . . . "The delicately balanced sequential processes involved in normal mammalian reproduction are clearly attackable. Our objective is to disrupt them in such a way that no physiological cost to the organism is involved. That objective will undoubtedly be attained by careful scientific investigation."

It is sobering to reflect that 24 years later the highly desirable aim of doing no harm has not been achieved.

Field trials

It had now become clear to Pincus and Rock that the time had come for extensive clinical testing to be carried

out. Perhaps with Margaret Sanger's words in mind, they looked for a poor community with high fertility and low educational standards—a community in desperate need of simple effective contraception. They chose Puerto Rico, a USA possession in the West Indies. Its capital, San Juan, had a medical school. Two doctors were assigned to the task of supervising the trials—Dr Edris Rice-Wray, a woman public health doctor, and a young gynaecologist, Dr Celso Ramon-Garcia. Ramon-Garcia, however, remained in San Juan for only a few weeks longer. He persuaded Pincus to allow him to work at the Worcester Foundation, and there, with Chang, Rock, and Pincus, he became one of the team of four with whom the Pill will always be associated.

The Pill that was to be used in large-scale trials in Puerto Rico was norethynodrel produced by Searle. It is not clear why norethisterone was left out. One possible reason was that Syntex was solely a manufacturing company, which at that time had no marketing division. Another reason may have been that Pincus had for many years been retained as a biology consultant by Searle.

The oestrogen 'impurity'

Small field trials began in Puerto Rico with Searle's norethynodrel—in other words, a Pill containing only a progestogen, or so Pincus and his colleagues intended and believed. The first results showed the high contraceptive effectiveness of the product. Then Searle's chemists became aware that their norethynodrel was contaminated with small quantities of an oestrogen, and they managed to get rid of the impurity. Immediately things began to go wrong. Breakthrough bleeding started to occur, and so did accidental pregnancies. It was quickly realized that a small quantity of oestrogen was necessary for maximum effectiveness and cycle control. So they put back the oestrogen in precise doses and the classical combined oral contraceptive had been created. Searle called their first product 'Enovid'. It contained 10 milligrams of norethynodrel and 0·15 milligrams, or 150 micrograms, of mestranol. Pincus's intention of avoiding the use of oestrogen had been frustrated after all. 'Enovid' was licensed for use as a contraceptive by the American Food and Drug Administration in 1960, and the following year the Family Planning Association in Britain approved the Pill for use in its clinics.

The role of the Royal College of General Practitioners

By 1964 the Pill was widely used in the UK, and many authorities realized the importance of long-term monitoring of its effects. One doctor was convinced of the extraordinary opportunity of carrying out a prospective study in general practice. His name was Ekke Kuenssberg. As a member of Council of the Royal College of General Practitioners, and of its Research Committee, he repeatedly urged the College to begin the organization of such a study. History apparently never fails to repeat itself, and this clear-sighted innovator was met with the customary strong opposition from many Council members. Early in 1965, Dr Kuenssberg called a conference at 14 Princes Gate of various interested parties. The outside experts were not at all encouraging.

The project continued to be discussed at meetings of the Research Committee, to which I had been co-opted in 1964. No real progress was made until an extraordinary meeting was called in December 1965. It seemed likely that a working party would then be formed. I had a long-term interest in family planning, having started a clinic in my own practice in 1957 at a time when contraception was by no means a respectable subject. Before the special meeting, I had written to Donald Crombie, who was then Chairman of the Research Committee, expressing my interest in serving on the proposed working party. The meeting duly took place, and it was finally agreed that a study should be planned. To my astonishment, during the meeting I was appointed recorder of the project. Nobody had asked me beforehand if I was willing to take on this task, or even if I thought I was capable of doing so. Admittedly, after I had been appointed, the chairman, apparently in a temporary fit of remorse, asked me if I realized what I was taking on. I replied, somewhat feebly, that I did. I was wrong, of course!

The case-control study

While preparations for the prospective study went ahead, Donald Crombie organized a retrospective study from the College's Birmingham Research Unit using the diagnostic registers kept by some general practitioners. This study was the first in the world to establish a statistically significant association between the use of oral contraceptives and venous thrombosis (RCGP, 1967).

The prospective study

Pilot trials

The prospective study required two and a half years of intensive preparation, during which four pilot trials of increasing size were carried out. The last pilot trial involved about 100 doctors, four nominated by each faculty. They recruited 1,200 patients between them. At this stage we submitted an application to the Medical Research Council for funding of the main study. Not surprisingly, they asked to see the results of the pilot trial before deciding. Time was now beginning to run out. There is no ideal time to launch a major general practice study, but the early spring of 1968 seemed a less objectionable time than any other. The use of oral contraceptives was now increasing so rapidly that there

was a real danger that if we waited until 1969 there would be too few non-users to recruit as control patients. The final pilot trial was started in September 1967. All the data were collected in early December. They were analysed, and I spent the whole of Christmas writing a report, which was delivered to the Medical Research Council by the end of the month.

There followed a prolonged silence. By mid-February I could no longer contain my anxiety. Too apprehensive to enquire myself, I persuaded Professor Alwyn Smith, who had become principal epidemiological adviser to the working party, to telephone the Medical Research Council for me. He rang back a few hours later. The project had been approved in full, subject to satisfactory progress after 18 months.

At this point, the total resources of the study consisted of a part-time secretary and a rather battered typewriter. Six weeks later, we had a manageress and secretary, a suite of offices, £14,000 worth of office and technical machinery, tens of thousands of carefully designed and printed documents, and 1,400 general practitioners ready to start recruiting patients.

Support from the pharmaceutical industry

This happy story of the pilot phase conceals a very real dilemma, which still has not been satisfactorily resolved. Before large-scale funding could even be considered, a great deal of money had to be spent. Although the then Research Foundation Board had contributed, the pilot trials were far beyond the financial resources of the College. Fortunately, we were saved by the assistance of all the UK pharmaceutical companies who marketed oral contraceptives. They provided the bulk of the cost of the pilot trials, and have continued to contribute throughout the study.

Although their contribution to the main study never amounted to more than three to four per cent of our expenditure, we could not have conducted it without their help, because the Medical Research Council is unable to pay for certain services which the host organization is expected to provide. Amongst the most important of these are the rent and rates of the offices.

In spite of the small proportion of money provided by the pharmaceutical companies, whenever we have reported findings favourable to the Pill there has always been someone who has accused us of bias. In fact none of the companies have ever seen any of our reports earlier than a day or two before publication at the same time that they were released to the press; nor have they ever expected to do so. They have also given me a great deal of scientific advice and support that would have been difficult to obtain elsewhere.

The main study

Our first office was on the first floor of a building near the centre of Manchester. One of its attractions was a Spanish restaurant in the basement, where an excellent three-course lunch was served for the rather quaint price of ten shillings and sixpence. In 1971, we remodelled our practice building, and the Research Unit was accommodated in it. We now employ 16 full-time staff, and I have two general practitioner colleagues who, like myself, work part time in the Unit.

Important publications

So far, there have been two clear high-spots in our publications. The interim report *Oral Contraceptives and Health* was published in 1974 (RCGP, 1974) and received widespread publicity in the news media. It provided the first opportunity to examine total reported morbidity in Pill users, and on the evidence then available the benefits seemed to outweigh the risks for the majority of women.

Three years later, our report (RCGP Oral Contraception Study, 1977a) on the increased risks of death due to vascular disease, confirming as it did mounting evidence from other studies (Collaborative Group for the Study of Stroke in Young Women, 1973; Shapiro, 1975; Beral, 1976; Mann *et al.*, 1976; Vessey *et al.*, 1977), led to an important change in clinical practice. We found a materially increased risk in women over the age of 35. This risk particularly applied to women who smoked cigarettes, and it appeared to be related to continuous use of the Pill for more than five years. The Presidents of the two Colleges most concerned jointly issued guidelines for the profession (Kuenssberg and Dewhurst, 1977), and these have had a substantial influence, at least throughout the western world, and accelerated an already apparent downward trend in the use of the Pill.

Progestogen effects

A much less well acknowledged observation of ours may, I believe, come to be recognized as the most important. Ever since Pincus decided to develop a progestogen rather than an oestrogen Pill, the oestrogen has been attributed with all the adverse effects and the progestogen has been considered blameless. In our 1974 report (RCGP, 1974) we showed that the rate of reporting of several diseases was related to the dose of progestogen in the combined Pill. The most important example was hypertension (Figure 1) and we could find no evidence that the incidence of hypertension in Pill users was related to the dose of the oestrogen component. Neither of these observations was wholly convincing, because the oestrogen and the progestogen do not act independently in the body. The biological effect of each is strongly influenced by the other (Edgren and Sturtevant, 1976). Moreover, there were nine different progestogens in varying doses and of varying potencies. Simply to combine the doses of the different preparations did not have much meaning.

The 'ovlars'

We then realized that we had been presented, by chance, with the opportunity of making valid comparisons of

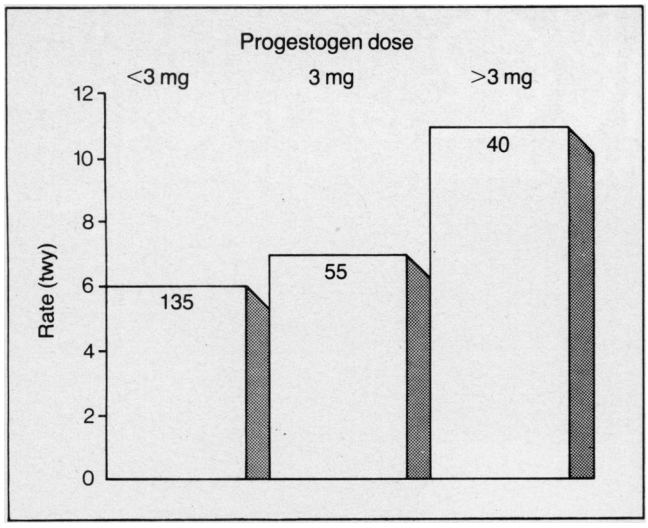

Figure 1. *Hypertension—1974. The number of cases is shown on the column; twy: thousand women years.*

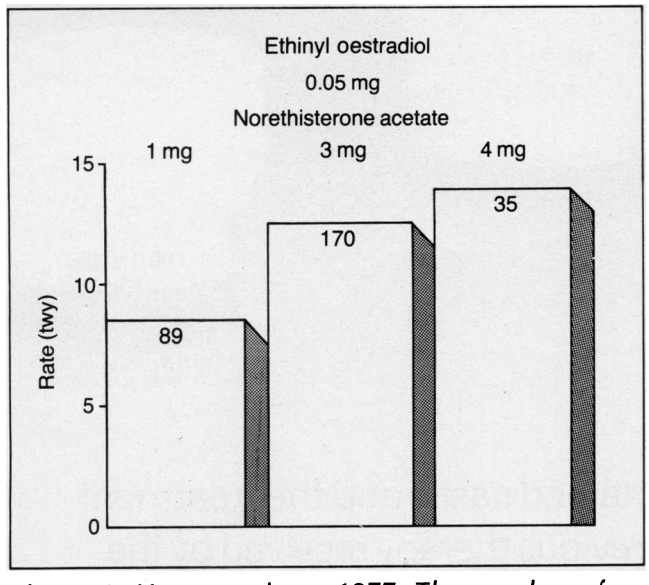

Figure 2. *Hypertension—1977. The number of cases is shown on the columns; twy: thousand women years.*

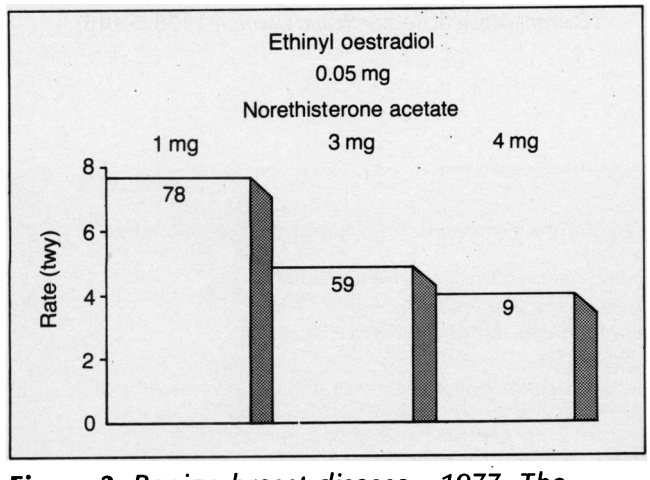

Figure 3. *Benign breast disease—1977. The number of cases is shown on the columns; twy: thousand women years.*

progestogen dose. Three brands of oral contraceptives, 'Minovlar', 'Gynovlar', and 'Anovlar', were in common use, so that we had substantial data on them, and all three were manufactured by the same pharmaceutical company and made into tablets with the same inert substances to provide bulk. This means that the active hormones are absorbed and dispersed in the body in an identical manner. The three brands contain the same dose of the same oestrogen, and different doses of the same progestogen. Any differences in their effects in similar populations could, therefore, be attributed to differences in the dose of the progestogen. In 1977 (RCGP Oral Contraception Study, 1977b) we showed that there was an increasing incidence of hypertension with increasing dose of the progestogen norethisterone acetate (Figure 2). We also showed that the protective effect of the Pill on benign breast disease was associated with the progestogen (Figure 3). No longer could it be assumed that the progestogen had no important influence on oral contraceptive side-effects, but remarkably little notice was taken of this observation.

The characteristics of the women taking the three brands were very similar up to 1976, when these analyses were carried out. Many new brands containing doses of oestrogen lower than 50 micrograms have come into common use since then, and the shift by some women to the new brands meant that some differences in the characteristics of women using 'Minovlar', 'Gynovlar', and 'Anovlar' emerged.

New evidence of progestogen effects

We know that age, cigarette smoking, and duration of use are the most important characteristics having an effect on the development of vascular disease in oral contraceptive users, so that in updating our analyses and examining the effects of other brands, we have standardized the results for these three variables. Our most recent data, standardized in this way, show that the rate of reporting of hypertension remains related to the dose of the progestogen (Figure 4).

Towards the end of their recommendations about the use of the Pill (Kuenssberg and Dewhurst, 1977), the Presidents commented: "We are unable to determine from present evidence whether oral contraceptives containing lower doses of oestrogen confer any advantage over those containing 50 micrograms." This was included for two reasons. First, because it was true, and secondly because we were already suspicious that the use of a lower dose of oestrogen with a new progestogen called levonorgestrel, that was many times more potent than norethisterone acetate, might not be an improvement. So we were particularly interested to observe the effects of these new brands. Because the rate of reporting of hypertension has varied at different periods of the study, it is only valid to compare brands in use over the same period of time (Figure 4). It is clear that there is no obvious advantage in the use of brands

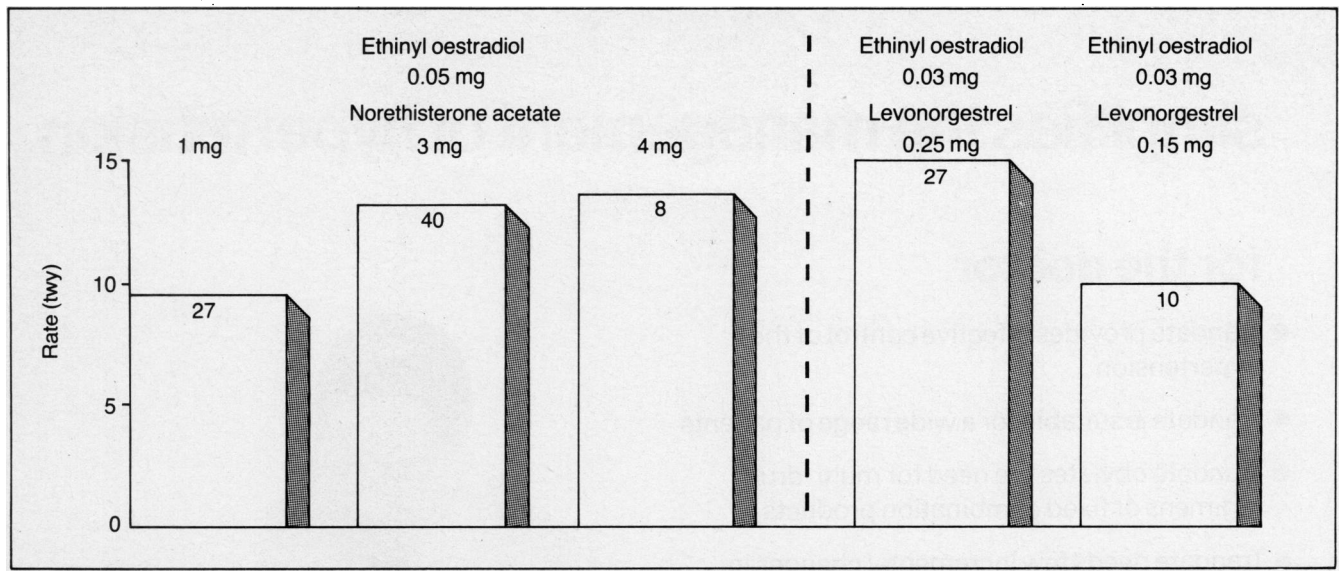

Figure 4. *Hypertension—January 1975 to March 1980. The number of cases is shown on the columns; twy: thousand women years.*

containing 0·25 milligrams of levonorgestrel, though the number of cases is too small to conclude that it has a worse effect. The brands containing 0·15 milligrams of levonorgestrel are associated with an incidence of hypertension similar to 'Minovlar'. Unfortunately, we have insufficient data so far to examine the effects of low oestrogen brands containing norethisterone or other progestogens.

Pill-induced hypertension is reversible, and usually the elevation of blood pressure is small. It is much more important to see if there are any differences between brands in their effects on the potentially dangerous arterial diseases. Fortunately these are uncommon, and so to obtain larger numbers we have had to combine the total reported circulatory diseases—ischaemic heart disease, cerebrovascular disease, and peripheral vascular disease. We have left out hypertension because the much larger number of these cases would swamp the effects of the other vascular diseases, and we can examine them separately.

Once again (Figure 5) we see a significant relationship to the progestogen dose in the strictly comparable brands. As in hypertension, it is of great interest to compare the rate of arterial disease in these brands with other brands, old and new. There were no cases at all reported with levonorgestrel brands containing the 0·15 milligram dose, so these cannot be assessed. It is of great interest, however, that the rate of reporting associated with the 0·25 milligram levonorgestrel brands (which contain low doses of oestrogen) is very similar to the reported rate of arterial disease occurring during the use of two old brands—'Ovulen' and 'Lyndiol', which contain what has now come to be regarded as a high-dose oestrogen (0·1 milligram in 'Ovulen' and 0·075 milligrams in 'Lyndiol').

With the low number of cases occurring with any one brand, it is not yet possible to prove which is the safest. I hope I have shown, however, that we must consider very carefully the progestogen content of an oral contraceptive, and the relative potency of the oestrogen and the progestogen it contains.

Lipid metabolism

I now have to make an apparent digression to describe the effect of sex hormones on lipid metabolism. Oestrogens and progestogens, both natural and synthetic, as well as many other hormones, are called ster*oids* because they are *like* sterols. The most important sterol in the human metabolism is cholesterol. It shares with the sex steroids the familiar structure of the four carbon rings. Indeed, natural oestrogens and progesterone are derived from cholesterol in the human body. Since the body always strives to maintain an equilibrium, it is not surprising that the taking of additional oestrogens and progestogens has a compensatory effect on cholesterol, and it was recognized many years ago that the Pill causes changes in cholesterol and in other fatty substances in the blood (Stokes and Wynn, 1971).

Blood is a water-based fluid, and fats will not dissolve in water, so that lipids circulate in the blood in the form of highly complex particles of varying sizes containing lipids and proteins. These are called lipoproteins (Figure 6). The largest particles, the chylomicrons, carry digested fat from the alimentary tract to the liver, and they appear in the blood only for a short time after a meal. The other lipoproteins appear in varying sizes. Cholesterol is the heaviest of the molecules in the lipoproteins, and the smallest particles contain the

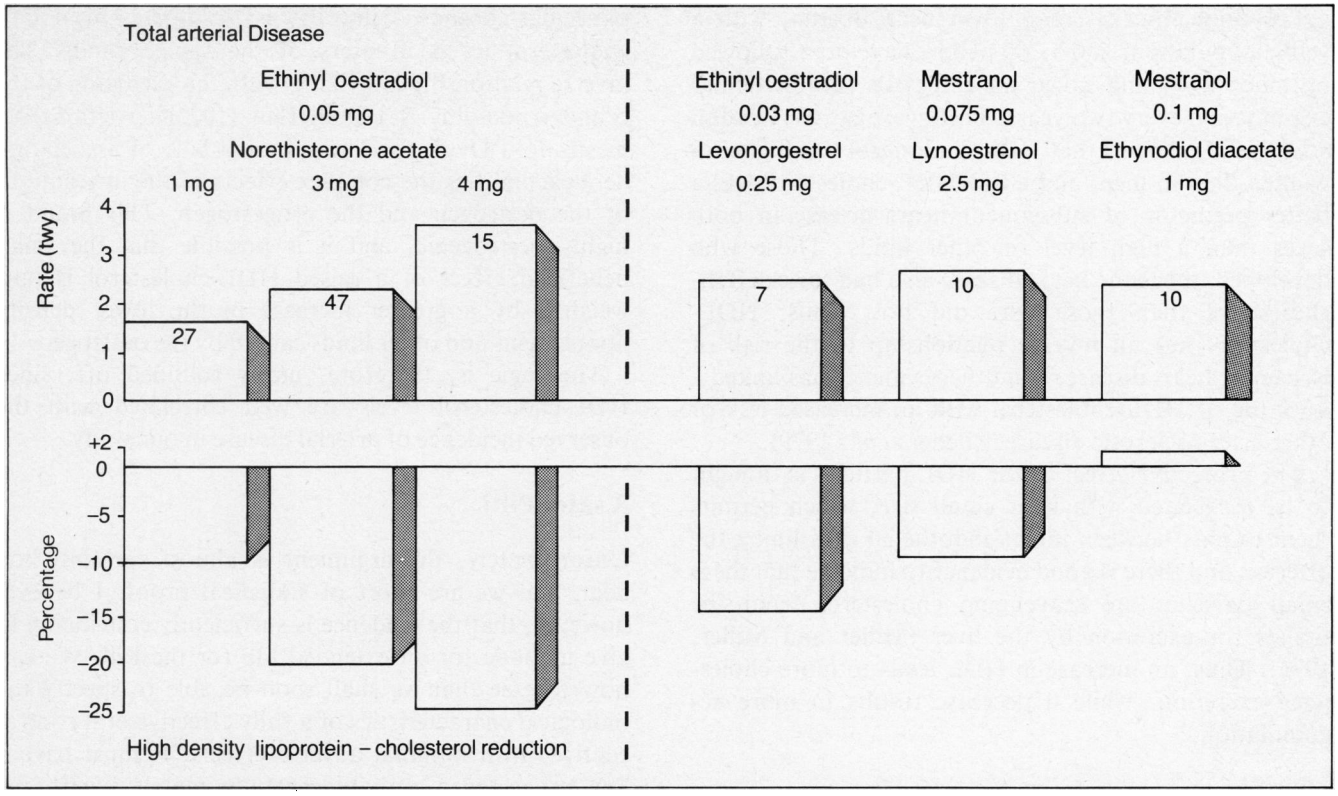

Figure 5. *Total arterial disease and high density lipoprotein–cholesterol reduction. The number of cases is shown on the columns; twy: thousand women years.*

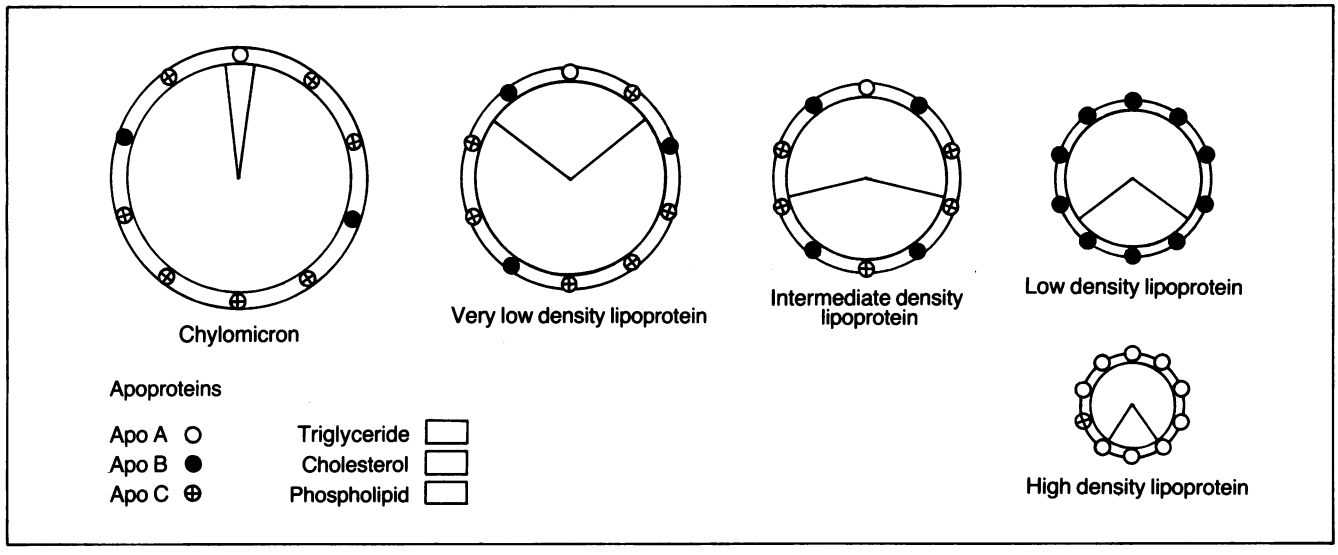

Figure 6. *Size and composition of lipoproteins. (This figure is reproduced from an article by Dr Maurice Stone which appeared in the February 1978 issue of Modern Medicine.)*

highest proportion of cholesterol. They are, therefore, the most dense, and are referred to as high density lipoproteins (HDL). An estimate of the cholesterol contained in the smallest particles is, therefore, called HDL-cholesterol.

The other particles are of increasing size and decreasing proportion of cholesterol, and they are called, logically enough, low density, intermediate density, and very low density lipoproteins.

HDL-cholesterol

Everybody knows that too much cholesterol is undesirable, but in 1951 Barr and his colleagues suggested that an excess of HDL, as opposed to the larger particles, was actually an advantage. This observation was largely forgotten or ignored until 1977 when the investigators from the Framingham Heart Disease Study confirmed and extended the observation.

Framingham is a small town near Boston, with a stable population, and 5,209 people have been followed up since 1948 and given an extensive cardiovascular examination every two years. The investigators (Gordon *et al.*, 1977) showed that HDL-cholesterol was higher in women than in men, and a low HDL-cholesterol was a better predictor of subsequent heart disease in both sexes than a high level of other lipids. Those who developed ischaemic heart disease also had lower HDL-cholesterol than those who did not. Thus, HDL-cholesterol has an inverse relationship to the risk of ischaemic heart disease, and other evidence has linked a lowering of HDL-cholesterol with an increased risk of other arteriosclerotic disease (Zilcher *et al.*, 1979).

The protective effect of the HDL particles is thought to be associated with their small size, which permits them to pass between intact endothelial cells lining the arteries, and there is good evidence to indicate that these small particles are scavenging cholesterol from the tissues for excretion by the liver (Miller and Miller, 1975). Thus, an increase in HDL leads to more cholesterol excretion, while a decrease results in more accumulation.

HDL-cholesterol and oral contraceptives

Several workers have shown that women taking oral contraceptives tend to have lower levels of HDL-cholesterol than age-matched non-users (e.g. Arntzenius *et al.*, 1978; Roossner, 1978). More recently, investigators have been attempting to determine the separate effect of the oestrogen and the progestogen components of the Pill. I was present at a conference in Washington in May 1979, called to discuss the results. There was a consensus that oestrogens tend to increase both HDL and lower density lipoproteins, while progestogens result in a decrease in HDL-cholesterol (Bradley *et al.*, 1978; Johansson *et al.*, 1979; Nikkila, 1979).

So the evidence from numerous sources around the world is accumulating to provide a persuasive story. We have shown that the progestogen content of the Pill is associated with the incidence of vascular disease. Low HDL-cholesterol is linked with an increased risk of arteriosclerosis. Progestogens have been shown to cause lowering of HDL-cholesterol.

At the Deakin University, Geelong, Australia, Michael Briggs, Professor of Human Biology, measured HDL-cholesterol levels in women taking a wide range of commercially available oral contraceptives (Briggs, 1979). Figure 5 shows the results he observed in women taking some of the brands represented in our own data. Briggs compares changes in HDL-cholesterol with the mean levels in a large group of women not using the Pill. The most important results are in the three brands which we have used for elucidating progestogen effects, since the depression of HDL-cholesterol is clearly strongly associated with the progestogen dose.

For the last step in the argument we can compare the incidence of arterial disease in our study in users of particular brands with Briggs' estimate of HDL-cholesterol levels in users of the same brands. The inverse relationship is striking, with the exception of the brand containing 0·1 milligram (100 micrograms) of mestranol ('Ovulen'). The apparent lack of association here exemplifies the complex effects of the interactions of the oestrogen and the progestogen. This brand is highly oestrogenic, and it is possible that the small beneficial effect of a raised HDL-cholesterol is outweighed by a greater increase in the lower density lipoproteins and other lipids caused by the oestrogen.

The logic is, therefore, nicely rounded off, since HDL-cholesterol levels are well correlated with the observed incidence of arterial disease in our study.

A safer Pill?

Unfortunately, the argument is almost certainly too neat, and we are short of statistical proof. I believe, however, that the evidence is sufficiently convincing to give us hope for an extended life for the Pill. We can now foresee that we shall soon be able to specify the biological characteristics of a fully effective oral contraceptive, with minimal adverse effects. It must have a low progestogen activity carefully matched with the oestrogen activity so as to provide contraceptive effectiveness and the least metabolic change (Shelton and Petitti, 1978; Larsson-Cohn *et al.*, 1979).

The specification may well demand some new molecular manipulation, both of the oestrogen and the progestogen. We cannot wait another 20 years to see if they cause serious disease, but if we can confirm the validity of the association with lipoprotein changes they can rapidly be tested for potential adverse effects on the vascular system, which are undoubtedly the most important unwanted reactions of current preparations.

In addition to developing a low-risk Pill we shall continue to learn more precise ways of identifying women with higher than average risk. And so a safer Pill will be complemented with safer use.

Sir James Mackenzie

This lecture commemorates the achievements of James Mackenzie, whose outstanding contribution to cardiology resulted from his solo work in general practice in Burnley, and to a much lesser extent from his work as a famous cardiologist in London. At the end of his career Mackenzie wanted to return to general practice research, and he set up his Institute in St Andrews (Mair, 1973). He intended to persuade local practitioners to pool the resources of their own practices, each of which was too small to provide enough data for the valid surveys of the early stages of disease that Mackenzie planned. This work did not succeed. There may be several reasons for this failure, but I have no doubt that one of them was the lack of a recognized academic association and common purpose for general practitioners. We have indeed been fortunate that we now

have such a body, which has provided us with unrivalled research opportunities—the Royal College of General Practitioners.

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Sterilization

Four hundred and six women—about one fifth of those requesting an induced abortion and sterilization over a 33-month period—volunteered to be allocated randomly either to a concurrent induced abortion/sterilization group or a group which was sterilized six weeks after abortion. The abortion-attributable and sterilization-attributable complication rates of 3·8 per cent and 5·2 per cent respectively for the concurrent group did not differ significantly from the 6·7 per cent and 6·9 per cent rates for the interval group. The estimated two per cent to 10 per cent of women who would have changed their minds must be set against the four per cent of women who became pregnant again before being sterilized. Efforts should be made to identify women likely to regret sterilization.

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