

DOCTORS inside the drug company manufacturing the most widely used hormone pregnancy test in Britain were so worried by evidence of its possible damage to unborn children that they wanted to withdraw the drug 10 years ago. But the parent company, Schering AG of Berlin, refused. Last week, the drug—Primodos—was still in chemists' shops in this country.

Internal correspondence from the British company, Schering Chemicals Ltd, of Burgess Hill in Sussex, has come into the hands of The Sunday Times.

Three years ago, this newspaper pointed to the failure of the Government-appointed drug safety committee to take action against Primodos. Now, the correspondence reveals that senior executives of the British company were so worried by their German parent's attitude that, again as early as mid-1968, they virtually invited the safety committee to take action. The committee did nothing.

In the intervening decade, a million and a half women in Britain have taken hormone pregnancy tests. The number of deformed children born as a consequence is estimated to run into thousands.

THE FIRST concrete evidence that sex hormones might cause human birth defects came in October 1967. Dr Isabel Gal, a research worker at Queen Mary's Hospital for Children at Carshalton in Surrey, discovered that women who had spina bifida babies were more likely than women with normal babies to have used hormone pregnancy tests. As well as that dreadful spine defect, Dr Gal found babies born to women taking the drugs were more likely to have hydrocephalus (swelling of the brain).

Dr Gal's work was the first pointer to human consequences. And nowhere was her report read with more concern than at the offices of Schering Chemicals Ltd, at Burgess Hill in Sussex.

For Schering not only manufactured Primodos, the most widely used of those pregnancy testing kits. It was also the company which had launched the oral contraceptive pill in Europe—and those pills contained, in different mixtures and strengths, the same hormones as the pregnancy tests.

Gal's figures only related to women in the London area. But Schering's research director, Dr Michael Briggs, had wider figures to work on. He had the sales of Primodos throughout Britain. And, because British medical statistics are very good, he had detailed breakdowns of all birth deformities recorded across the country. To refine the sales pattern, Briggs also got the sales figures of Primodos' nearest rival in the pregnancy testing market, the drug Amenorone forte, manufactured by the French firm Roussel.

Briggs sent all these figures to Dennis Cooke, a mathematics lecturer at the University of Sussex. On November 2, 1967, Cooke reported a "strong correlation" between the incidence of malformations and the sales of the drugs.

Briggs was not his own master.

CAUTION S4

amenorone forte

PRIMODOS

NG AG

PRIMODOS

These drugs can deform babies but mothers are not warned

By Oliver Gillie, Medical Correspondent

BRIGGS AND his colleagues at Burgess Hill realised the scale of the problem they faced. Primodos had been on sale in Britain since 1958. By 1968, four out of every ten British women who thought they might be pregnant were using hormone tests. Hundreds of thousands of babies were at risk. Then there were the implications for millions of women taking the Pill.

May 1975: but the companies knew since 1967

The British end of Schering is a wholly-owned subsidiary of Schering AG of Berlin. So Briggs passed the information—and his concern—to Berlin.

Throughout what followed, Schering's German head office took a consistent line: it attacked uncomfortable news, and tried to protect Primodos.

Thus, Berlin's first defence against Briggs's news was to respond that, in Germany, sales of the drug did not correlate with birth abnormalities. But when Briggs sent the German figures to Cooke, the mathematician pointed out that, unlike those in Britain, German statistics do not record all birth abnormalities, only deaths from abnormalities. Berlin's calculations were misleading.

BRIGGS AND his colleagues at Burgess Hill realised the scale of the problem they faced. Primodos had been on sale in Britain since 1958. By 1968, four out of every ten British women who thought they might be pregnant were using hormone tests. Hundreds of thousands of babies were at risk. Then there were the implications for millions of women taking the Pill.

On June 6, 1968, Dr Alan Pitchford and Dr Patrick Eye, medical directors of Schering Chemicals in Britain, wrote to Dr J. Friebe, a medical adviser of the company in Berlin, urging: "... we must reach a decision regarding our own product Primodos and its possible relationship to foetal abnormalities."

"As manufacturers it is our moral duty," they said, "to do all possible to ensure the safety of the preparations which we market. Where suspicion of this kind has been aroused by an investigator whose integrity and ability cannot lightly be challenged, the onus of proof must lie with us. It is for us to establish that the drug is safe to use. . . ." As an interim measure

they said, they had stopped promoting the drug.

Promptly, on June 14, Friebe replied with Berlin's second line of defence. Studies were in progress, he said, to see if the drugs caused abnormalities in offspring of pregnant mice and rabbits.

This too was incorrect, as Briggs and his colleagues later discovered. What was being tested was Schering's range of contraceptive pills: Anovlar and Gynovlar. In any case, these tests proved inconclusive for technical reasons. (It was because the drug laws of the time did not require it—that the contraceptive pill had not been tested on animals before being marketed.)

Balked by Berlin, Pitchford then turned to the officially-appointed body in Britain which might have been expected to support him, the Committee on Safety of Drugs. But despite its wide remit to monitor drug side-effects and protect the public, the committee proved a poor ally.

Though it was "unhappy" about the use of hormone pregnancy tests, he was told, there was "insufficient information for any definite action to be taken."

Evidence continued to accumulate however. In January 1969, a survey by the Royal College of General Practitioners revealed an apparent increase in abortions among women taking the hormone drugs. The college circulated the survey privately among drug companies, and, remarkably, even though the author of the survey, Dr Norman Dean, was sufficiently alarmed by his results to recommend withdrawal of the drug, the current president of the college, Dr Ekkehard von Kuenssberg, felt able to write to Schering, "I hope you won't feel worried" by what he called Dean's "personal opinion."

• Oliver Gillie wrote the story illustrated left ten years ago. Now he reveals . . .

Drug company ignored deformity risk for 10 years

• Primodos 1 tablet on each of two occasions. Bleeding follows in 3-6 (rarely as long as 12) days. If there is no pregnancy. An existing pregnancy is not affected by Primodos.

July 1969: Schering's booklet to doctors



Sir Eric Scowen: head of the drug committee that took no action



Dr Kue Schering to stop

He need not have feared, Berlin remained unruffled. On February 11, the Schering doctors Friebe and Ursula Lachnit concluded: "... the results are, in our opinion, by no means alarming and in particular we do not see any basis for Dr Dean's recommendation to withdraw Primodos from usage."

Nine years later, that survey remains unpublished. But the college admits that further analysis confirms its conclusion that the hormone test do cause abortions.

Again, Pitchford appealed to the Committee on Safety of Drugs—again, to no avail. A stand by the committee at this point would immeasurably have strengthened Pitchford's appeal to Berlin, to take the drug off the market. Instead, in February 1969, one of the committee's search officers, Dr William Inman, told Pitchford: "The data you have so far are of

unhelpful "on". The committee has fore it was ment on a highest m proof, which ignored approach risks of a anced aga fact was 1960s, how unnecessary urine tests

Schering 1969. Friebe: justification Primodos diagnosis of side extremely results of studies an point clear that Prim with a pointed to Schering attention to tion between Primodos oral contr

Gallie wrote the story illustrated left three
Now he reveals...

Drug company ignored fertility risk for 10 years



Dr Isabel Gal: found the first cases

Primodos: 1 tablet on each of two consecutive days.
Bleeding follows in 3-6 (rarely as long as 10) days; if
there is no pregnancy. An existing pregnancy is un-
affected by Primodos.

July 1969: Schering's booklet to doctors denies the risk



Sir Eric Scowen: head of the
drug committee that took no
action



Dr Kuenssberg: advised
Schering not to take advice
to stop drug

"We need not have feared, Berlin remained unruffled. On February 11, the Schering doctors Friebe and Ursula Lachmann concluded: "... the results are, in our opinion, by no means alarming and in particular we do not see any indication to withdraw Primodos from usage."

Nine years later, that survey remains unpublished. But the college admits that further analysis confirms its conclusion that the hormone test do cause abortions.

Again, Pitchford appealed to the Committee on Safety of Drugs—again, to no avail. A stand by the committee at this point would immeasurably have strengthened Pitchford's appeal to Berlin, to take the drug off the market. Instead, in February 1969, one of the committee's research officers, Dr William Inman, told Pitchford: "The data you have so far are quite

unhelpful in coming to a decision "on withdrawal."

The ineffectiveness of the committee had a simple cause. Before it was willing to pass judgement on a drug, it demanded the highest standards of scientific proof, which was creditable, but ignored the common sense approach that the possibility risks of a drug have to be balanced against its value. And the fact was that, since the early 1960s, hormone tests had been unnecessary because the simpler urine tests was available.

Schering knew this. In July 1969, Pitchford wrote to Friebe: "There is very little justification for the use of Primodos when more rapid diagnosis can be made by means of slide or tube tests... it is extremely disturbing that the results of studies, human studies and animal studies, all point clearly to the possibility that Primodos may interfere with a pregnancy..." He pointed to the commercial risk Schering was running: "If attention is drawn to the association between the drug used in Primodos and those used in oral contraceptives, the commercial consequences could be extremely serious."

reach the public. For in the same month, July 1969, in which Pitchford was writing so anxiously to Berlin, Schering issued a booklet for British doctors called Synopsis of Hormone Therapy in the Female. It declared: "An existing pregnancy is unaffected by Primodos." Such an unqualified statement had no justification.

BY NOW, Schering's main rival, Roussel, had dropped—in May 1969—its description of its own drug, Amenorrone Forte, as a hormone pregnancy test. Now, Roussel referred to it only as a treatment for amenorrhea (the absence of period).

The possible reason for this was reported to Berlin by Pitchford on August 7, 1969. Roussel, he said, had been looking at the effects of the drugs: "A long term study in humans is nearing completion, a computer analysis of which should be available shortly. An interim analysis revealed statistically significant abnormalities in patients receiving hormone pregnancy tests."

Asked about this study recently, Dr Norman Eve, the present medical adviser to Roussel, at first denied that any such study had been made but finally agreed that a study had been undertaken. He said that it showed no risk.

Whatever the findings, they did not persuade Schering to follow Roussel's example. And not until 1970 did any official body—and then not the Committee on Safety of Drugs but another group, the McGregor Committee on labelling of drugs—take action against Schering. McGregor got Schering to follow Roussel—not because of the risk, simply because McGregor at last recognised that the hormone test was obsolete and unnecessary. Even in this, however, the authorities were inconsistent: another hormone preparation, British Drug Houses' Secrolyl, was allowed to be described as a pregnancy testing drug until 1975.

Other countries were less faltering. The first to act were the Swedes, who banned the drugs for pregnancy tests in 1970. The Finns followed in 1971. In Re-

until 1972; Primodos remained the market leader; and Schering knew, from their own market research as early as 1968, that three-quarters of the Primodos prescribed was for pregnancy testing rather than as a treatment for absent periods. Yet Schering took no positive steps—nor did the authorities require any—to warn doctors.

EVEN when, in January 1973, Schering in Berlin finally recommended to all its subsidiary companies that they cease to promote Primodos tablets, the companies were instructed to tell doctors that the "Schering expert panel" was of the opinion that: "Despite the exceptionally widespread use of this preparation, there have specifically been no adverse effects occurring till now upon the embryo or foetus of an existing pregnancy." This statement totally ignored all the scientific evidence.

How serious that evidence was the American watchdog, the Food and Drugs Administration, powerfully summarised in January 1975. It warned that sex hormones "should not be used in early pregnancy for any purpose. Such use of these hormones may seriously damage the foetus... including heart and limb reduction defects."

Yet in Britain, even though the Committee on Safety of Drugs had by now been superseded by the Committee on Safety of Medicines with stronger powers, the authorities took no action. They did nothing even when, in April 1975, two of the committee's staff, Dr Gillian Greenberg and Dr William Inman, published research data showing that women taking the drugs had a greater proportion of abnormal babies. They concluded: "There is little justification for the continued use of [these] pregnancy tests when alternative methods are available."

NOT UNTIL The Sunday Times had drawn attention in May 1975 to the contradiction in its actions did the Committee on Safety of Medicines finally send out a warning to doctors. Schering at once responded by attaching a red warning label to the Primodos packets available in Britain.

Even that was clearly inadequate. According to independent market research figures, sales of Primodos and other hormone pregnancy test drugs in Britain fell by a third in Britain following these warnings. Yet some 40,000 women were still prescribed the drugs as a pregnancy test in 1975, and some 25,000 had it in 1976. Even last year—after a second warning from the committee—6,000 women in Britain took the drug as a pregnancy test. And though Schering now say that the drug has been "discontinued" in Britain for "economic reasons," The Sunday Times obtained Primodos on prescription two weeks ago.

Moreover, sales of Primodos worldwide grossed £4 million last year. And Schering acknowledged that they did not attach the red warning labels to Primodos sold outside Britain.

Schering say that in their opinion there is no substantive evidence to date to support the "hypothesis" that hormone pregnancy tests cause abnormalities at birth. They quote a statement by the German Endocrinological Society, saying that