# Papers and Originals

## Recognition of Unwanted Drug Effects*

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### Early Methods of Detection

Concern about the side-effects of drugs and the best way of recognizing them has been felt for many years, and has increased with the increasing competence of the pharmaceutical industry. At first it seemed adequate to leave the problem in the hands of pharmacologists and the physicians who used the new drugs in clinical practice. Gradually, however, it came to be realized that this was insufficient. In particular, it was appreciated that some reactions were so rare that individual physicians might never see more than one or two examples, and that, unless steps were taken to collate experience, important reactions—in the sense that they had serious consequences for the individual—might be missed.

The problem came to a head in the United States in 1952, when it was realized that chloramphenicol had caused scores of cases of aplastic anaemia and that it had taken three years to appreciate the potential toxicity of the drug. The American Medical Association reacted by appointing a study group to collect information about all cases of blood dyscrasia suspected of being caused by drugs or other chemicals, and after trying out a pilot scheme it established a registry for this purpose. Physicians were invited to report cases on a special form, and tabulations of the results were distributed twice a year to medical schools and interested organizations in the United States and abroad. Later a systematic review of the world literature was begun, and published reports were added. By May 1961 the results had proved so useful that the Association expanded the registry to include the collection of reports on adverse reactions of all types.

Six months later Dr. Lenz, of Hamburg, read a paper to a meeting of paediatricians in which he expressed concern at the large increase in the number of children referred to his clinic with phocomelia and other mesodermal deformities. The thalidomide epidemic had arrived, and the prevention of unwanted drug effects had become a matter of public concern throughout the world. In retrospect it is evident that the epidemic began in West Germany in 1959, three years after thalidomide was first marketed. Occasional cases of phocomelia had occurred previously, but the malformation was rare, and most West German paediatric clinics saw none at all during the 10 preceding years. Then 17 cases were seen in 10 clinics in 1959, 126 in 1960, and 477 in 1961. Many factors were considered as possible causes, but when Lenz investigated his patients retrospectively with a questionary, at least 20% of the mothers were found to have taken thalidomide in early pregnancy, a figure that was raised to 50% on more intensive interrogation. In contrast, none of 300 women who had given birth to normal infants were found to have taken the drug in the same period (Lenz, 1962).

Thalidomide was never used to the same extent in Britain, and the total number of affected children who survived long enough to be recorded in the national survey at the end of 1962 was about 300, less than a tenth of the estimated number in West Germany. As a result the numbers seen in any one clinic were extremely small, and Speirs (1962) and Kohler, Fisher, and Dunn (1962) were the only clinicians to recognize a local epidemic before the cause was discovered. Clear evidence was obtained, however, by examining the registers of congenital malformations that were kept for research purposes in Birmingham and Liverpool. These showed that an epidemic had occurred with a temporal distribution that corresponded with the supply of thalidomide to wholesalers after an interval of nine months (Smithells and Leck, 1963). Further evidence was also provided by the fact that both the consumption of thalidomide and the incidence of the characteristic malformations were appreciably greater in Liverpool than in Birmingham.

At this time no national machinery existed for the early detection of such an effect in Britain, and schemes were therefore proposed for the voluntary notification of all congenital malformations in newborn infants and for supervising the introduction of new drugs and monitoring their unwanted effects. Both schemes came into operation on 1 January 1964.

### Notification of Congenital Malformations

Congenital malformations are now notified, mainly by nurses and midwives, to medical officers of health, and the results are analysed centrally by the Registrar General. Medical officers of health are then told (1) if the number of cases of any specific malformation in their area significantly exceeds the number that would have been expected from the national average, or (2) if the trend in the numbers shows a significant increase over the previous six months. How valuable this system can be remains to be shown. A reasonable level of stability in the notification rate has already been obtained (Table I), but detection (or notification) is certainly not complete ; for example, the notified rate for congenital dislocation of the hip is about 4 per 10,000 live births, whereas the true figure is probably three or four times higher (Chief Medical

TABLE I.—*Frequency of Malformations Notified per* 10,000 *Live Births*

| Site | Notification Rate | | |
|---|---|---|---|
| | 1964 | 1965 | 1966 |
| Central nervous system | | 24·2 | 23·4 |
| Eye, ear | | 5·2 | 4·8 |
| Alimentary system | | 18·7 | 19·9 |
| Heart and great vessels | | 7·6 | 7·8 |
| Respiratory system | | 2·0 | 1·7 |
| Urogenital system | | 12·3 | 13·0 |
| Limbs | | 62·9 | 61·3 |
| Other skeleton | | 3·6 | 3·7 |
| Other systems | | 12·2 | 12·7 |
| Other malformations | | 9·1 | 9·9 |
| All sites | 164 | 157·9 | 158·3 |

* Marc Daniels Lecture given at the Royal College of Physicians of London on 8 January 1969.

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Officer of the Ministry of Health, 1968). Moreover, it will be difficult to know how fine a classification into types of malformation is justified by the nature of the material, and without fairly detailed division of the categories the change in the incidence of a specific malformation may easily be overlooked.

## Committee on Safety of Drugs

The machinery that was set up under the Committee on Safety of Drugs for reviewing the toxicity and efficacy of new drugs and new preparations is working smoothly and without causing any undue delay in their use. For these functions, however, precedents were already established, and the mode of working of the Subcommittees on Toxicity and on Clinical Trials and Therapeutic Efficacy presented no unusual difficulty. The situation facing the Subcommittee on Adverse Reactions was different. Many, perhaps most, of the important side-effects of a drug could be recognized in the normal course of practice by the physicians who first used it, and no special machinery was needed beyond that for reporting the results of the initial trials to the committee and for the rapid publication of later observations in the medical press. But what of the effects that occurred only in one out of 1,000 or more individuals ; when the drug was given in combination with another ; or after several years' use ? There was no body of experience on which the committee could draw for determining the best method of recognizing such effects, and it had to proceed slowly, trying out new procedures and modifying them in the light of its own experience.

In the event the subcommittee decided to rely on the voluntary submission of reports by individual doctors, and such estimates as it was able to make from existing sources of the frequency with which the drugs were used. The former are obtained by inviting all doctors to report on a standard yellow card " all reactions of a serious, uncommon, or unusual nature," and all reactions with new drugs " no matter how trivial." The estimates of drug usage are made from trade sources, and the monthly analysis is made by the Ministry's Pricing Bureau of 1 in 12 prescriptions written by a sample of about 1,000 general practitioners, the membership of which is changed regularly. Then, if suspicion is raised, one of the 48 part-time investigators employed by the subcommittee can visit the doctor who reported the case to obtain more detailed information.

The limitations of this system have been described by Professor Witts (1965), chairman of the subcommittee. In essence they are due to two facts. Firstly, reporting is incomplete, and the degree of incompleteness is unknown and variable—varying both from reaction to reaction and from time to time. In one year, for example, the total number of reactions reported per month varied from 150 to over 800 in the month following a letter from the committee to the medical and dental professions. Secondly, the committee is unable to determine either the number of patients given a drug or their distribution by sex and by age ; hence it is unable to estimate with any accuracy the incidence of the reported reaction for comparison with its normal incidence in ill patients or in the normal population. Witts (1965) discussed some of the possible alternatives, and it is evident that there is no easy solution. Certainly I am not able to suggest one. It may, however, be helpful to review some of the problems that have arisen, and to consider what arrangements might have enabled the existence (or absence) of particular risks to be confirmed more rapidly and perhaps with greater confidence.

## Adverse Reactions Necessitating Withdrawal

In the five years that have passed since the committee began its work reactions have been reported to four drugs which, in the light of the therapeutic value of the drugs, have been regarded as severe enough to justify their withdrawal (Inman, personal communication). Two had passed the initial screening of the Subcommittees on Toxicity and Clinical Trials. One drug had been included in a preparation for use on the skin of babies suffering from napkin rash. Reports were received of ulceration of the perineum following treatment which in several cases required extensive skin grafting. Another was a depot preparation of influenza vaccine. More than 100 local lesions were recorded, many of which resulted in sterile abscess or sinus formation. In both these cases the localization of the lesion to the site of application and its unusual severity left no doubt that it was due to the use of the agent.

With the other two drugs the effect was damage to the liver. Reports of jaundice, which was sometimes fatal, were received soon after the drugs were introduced ; and it was notable that the number of these reports greatly exceeded the number of reports of trivial side-effects which commonly accompany the introduction of a new drug. Crude estimates of the incidence of jaundice, based on the number of reports and the estimated sales figures, indicated that the minimum incidence was relatively high and the drugs were withdrawn. With one there was no experimental or other evidence to suggest that liver damage might be produced, and the risk was recognized only as a result of the practical experience of using the drug on a large scale. With the wisdom of hindsight it is now possible to see that some previous evidence of hepatotoxicity already existed for the other.

## Adverse Reactions Necessitating Caution

During this period many thousands of other " reactions " have been reported, the majority of which are likely to have been coincidental accompaniments of treatment rather than attributable to it. In several instances, however, the severity of the reaction and the evidence relating it to the drug have been sufficient for the committee to issue a warning, but the drugs have not been withdrawn because the risks have been thought to be less than the corresponding benefits. The drugs and the unwanted effects associated with them are summarized in Table II.

TABLE II.—*Warnings of Adverse Reactions Sent Out by Committee on Safety of Drugs*

| Drug | Adverse Reaction |
|---|---|
| Monoamine oxidase inhibitors .. | Episodes of hypertension. Liver damage (especially with hydrazine group) |
| Psychotropic drugs in general .. | Increased risks when given in combination |
| Antiarthritic drugs: | |
| Phenylbutazone, Oxyphenbutazone, Nifenazone .. .. | Blood dyscrasias. Liver damage. Peptic ulceration |
| Indomethacin .. .. .. | ? (caution advised) |
| Analgesic: mefenamic acid .. | Diarrhoea and gastrointestinal haemorrhage |
| Chloramphenicol .. .. .. | Blood dyscrasias |
| Aerosol bronchodilators .. .. | Risk of overdosage and (possibly) sudden death in asthma |

## Monoamine Oxidase Inhibitors

The first drugs which doctors were warned about were the monoamine oxidase inhibitors. Hypertensive attacks were described in 1955 when iproniazid was introduced for the treatment of tuberculosis (Ogilvie, 1955), and were rediscovered four years and again six years later when first nialamide (Davies, 1959) and then tranylcypromine (Lurie and Salzer, 1961) began to be used for the treatment of depression. By the beginning of 1963 over 40 cases had been reported, including several complicated by intracerebral haemorrhage or cardiac failure, and there was evidence that some attacks had been precipitated by the simultaneous use of sympathomimetics (see Sjöqvist, 1965).

The hypertensive crises lasted 10 minutes to six hours, and the symptoms associated with them were often thought to be

neurotic by the doctors who were called to see them—sometimes on the grounds that the patient was already suffering from neurosis but sometimes because the general practitioner was unaware that the patient was receiving medical treatment from a specialist. Some patients presented with subarachnoid haemorrhage and were regarded as having experienced the normal complication of a cerebral arterial aneurysm. In retrospect it seems probable that hypertensive crises were experienced by 8 to 10% of all patients on tranylcypromine (Blackwell, Marley, Price, and Taylor, 1967), though the manufacturers estimated that the figure was only 0·3%, on the basis of the replies to a questionary that they had circulated to psychiatrists (*British Medical Journal*, 1964a).

Several observers had noted that an attack might be precipitated by alcohol or a heavy meal, but the idea that it might be precipitated by cheese—and in particular by the amino-acids in cheese—was suggested by Mr. Rowe, a pharmacist, who observed the relationship in his wife (Blackwell *et al.*, 1967), and was confirmed by Blackwell (1963), who found that 8 out of 10 patients had eaten cheese within two hours of the onset of the attack. Subsequently he reported that he had also been able to precipitate an attack by giving cheese to a susceptible volunteer (Samuel and Blackwell, 1968).

Several other doctors reported similar experiences, and Read and Arora (1963) recalled that the association had been drawn to their attention the year before by a patient who had written describing her own attacks of migraine on the drug, and had added that "other patients experienced this as well after cheese but the doctors laughed at the idea."

Finally Asatoor, Levi, and Milne (1963) pointed out that it had been known for 50 years that cheese contained tyramine and that tyramine was capable of causing a rise in blood pressure and "excruciating headaches." They confirmed that the amount of tyramine in cheese was sufficient to produce the effect, and that it was normally metabolized and its end-products were excreted within a few hours. In the presence of the drug the metabolism of tyramine in the gut wall would be inhibited and noxious amounts absorbed (Elis, Laurence, Mattie, and Prichard, 1967).

The essential facts had therefore been known long before the monoamine oxidase inhibitors were introduced, and in retrospect there would seem to be no reason why their effects should not have been predicted.

## Pressurized Aerosols for Asthma

The warning about the use of aerosols containing sympathomimetics in the treatment of asthma was based on evidence of a different type. Inquiries began in April 1966, when Dr. Beryl Corner told the West of England Thoracic Society that the number of children dying from asthma had increased in Bristol and that the increase was most noticeable in children over 10 years of age (Smith, 1966). Dr. John Smith, consultant physician at the Birmingham Chest Clinic, was struck by the fact that a *decrease* had been reported by others, and he turned to the Registrar General's Statistical Reviews to see what the position was in England and Wales as a whole. These showed that the total number of deaths fell between 1950 and 1960 and then rose slightly until 1964. In children, however, the number remained constant until 1960, when it increased rapidly to three to four times the previous level (Smith, 1966). More detailed analysis showed that the increase was most marked at 10 to 14 years of age, and that it continued until 1966 (Speizer, Doll, and Heaf, 1968). By this time the mortality at these ages had increased seven times in seven years, and had come to account for 7% of all deaths. In the wider age range of 5 to 34 years the mortality had increased three times and had become higher than at any previous time in the past 100 years (Speizer and Doll, 1968). Similar, though generally less marked, changes were also found to have occurred in Australasia, Japan, Western Europe, and the United States.

Changes in national death rates are never easy to interpret, and the possibility has to be considered that they may be an artifact due to changes in the standard of diagnosis or in the method of classification. The diagnosis of asthma, however, is unlikely to be confused with any other diagnosis in the age groups under consideration, and Speizer, Doll, and Heaf (1968) were unable to find any evidence that such artificial factors could have been responsible for the increase in mortality. Data collected by the Royal College of General Practitioners (personal communication and Fry, 1962) indicated that the consultation rate for asthma had remained about constant over the past 10 years, and for this and other reasons it seemed probable that the increase in deaths reflected an increase in the severity of the disease.

In August 1965 Dr. M. J. Greenberg reported that eight of his patients had died suddenly following the excessive use of aerosol inhalers containing either isoprenaline or orciprenaline, and one possibility was that the pressurized type of inhaler, which had been used to an increasing extent every year since it was first introduced into Britain in 1960, was responsible for the increase in mortality. A temporal correlation of this sort, however, is a poor basis for drawing conclusions about cause and effect, and with Strang we tried to obtain more evidence by inquiring about the circumstances surrounding individual deaths (Speizer, Doll, Heaf, and Strang, 1968).

For this purpose the Registrar General provided copies of the entries relating to the 184 deaths that were attributed to asthma in young persons (aged 5 to 34 years) during a six-month period. Inquiries were then made of the general practitioners, hospital doctors, and pathologists who had treated the patients or examined them after death. Necropsy examination had been made in 124 cases (61% of the total), and the data confirmed that the overwhelming majority of patients had indeed suffered from, and died of, asthma. Corticosteroids and sympathomimetic preparations were the only drugs to have been used by most of the patients, and the latter—mainly isoprenaline and orciprenaline—had been used in the form of pressurized aerosols by 84%.

This evidence also was compatible with the idea that the aerosols were responsible; but it was not decisive, and it is difficult to see how any decisive evidence could have been obtained. Asthma is easy enough to recognize, but it is not easy to define its severity or to define groups of patients in whom the risk of death is both equal and high. And if such groups could have been defined, it would have been impossible to find one in which pressurized aerosols were not used. That the inhalation of sympathomimetics might contribute to death is pharmacologically possible, but on present knowledge it is not certain. Large amounts absorbed from the bronchi over a prolonged period might cause ventricular irritability and fatal arrhythmia; but the drug is metabolized quickly, and the mode of death seldom suggested that cardiac arrest had followed acute overdosage. Sometimes, as Palmer and Diament (1967) and others have shown, the inhaled bronchodilator may reduce airways obstruction without producing a corresponding improvement in arterial oxygenation, and so bring the patient nearer to respiratory insufficiency before he or his doctor asks for hospital admission. More significantly, perhaps, Paterson, Conolly, Davies, and Dollery (1968) have some evidence that a metabolite of isoprenaline may block $\beta$-adrenergic receptors, and so perhaps produce the opposite of the desired effect.

In these circumstances it was not difficult to think of the relationship; the problem was to see how it could be proved. In fact, the only method may be to act on the circumstantial evidence; limit the use of the drugs and see what happens.

What has actually happened is, in one respect, very satisfactory. The number of deaths reached a seasonal maximum in the first quarter of 1967 and then began to decline. Now,

within 18 months of the letter from Drs. Greenberg and Pines (1967) relating their personal experience of the danger of pressurized aerosols and within a year of the committee's warning on the subject, the death rate at ages 5 to 34 years has fallen from 250% above the 1959–60 level to only 50% above it. Interpretation of the changes is, however, still not clear. The sale of pressurized aerosols began to decline at the same time, but the rate of fall has been a good deal slower. It may be, of course, that there has been a greater reduction in excess use, but it also has to be borne in mind that doctors have become more aware that some patients live close to the limits of their ventilatory capacity, and have "simply learnt not to waste their breath by complaining." Cromoglycate has been introduced and has been used extensively in the past few months, and the use of corticosteroids has increased. The verdict must therefore remain not proved.

## Oral Contraceptives

No account has yet been given in the Committee's Adverse Reactions Series of the effects of oral contraceptives, but public statements about the risks of thromboembolism were made in 1967 and again in 1968.

The first report of a thromboembolic disorder in a woman taking an oral contraceptive was published in 1961 by Dr. W. M. Jordan, a general practitioner in Suffolk. The patient was a 40-year-old nurse who was given Enavid for the control of recurrent endometriosis. The treatment had to be abandoned after several weeks because of severe vomiting, and 10 days later (one week after the vomiting had stopped) she developed bilateral pulmonary embolism. Since then many hundreds of cases have been reported. Most of the reports describe deep vein thrombosis in the lower limbs or pulmonary embolism, but others describe cerebrovascular accidents, coronary thrombosis, mesenteric and other arterial thromboses, and the Budd–Chiari syndrome.

All these conditions also occur in young women who are not using oral contraceptives, and by themselves the reports provide no significant evidence that oral contraceptives could cause the diseases in question—except perhaps in the case of the extremely rare Budd–Chiari syndrome. Table III shows the number of reports of all the adverse effects of oral contraceptives that have been received by the Committee on Safety of Drugs since 1964. Even the fact that thromboembolism has been reported more frequently than any other condition carries little weight, as doctors are most likely to report those conditions that have already been given publicity.

Further evidence, therefore, was sought by using the reports to estimate the incidence of thromboembolism in women who were using the preparations. When this was done the manufacturers (Searle and Co., 1962) and the U.S. Food and Drug Administration (1963, 1966) in the United States and the Committee of Safety of Drugs (Cahal, 1965) in Britain all found either that the reported incidence was less than the normal incidence in women of similar ages or that it was so little more that the excess was not statistically significant. Little confidence could, however, be put in these comparisons, unless it could be shown that the reporting of thromboembolism on a voluntary basis was complete enough to provide an accurate picture of the situation.

TABLE III.—*Reactions to Oral Contraceptives Reported to Committee on Safety of Drugs 1964 to mid-1968* (Inman, personal communication)*

| Reaction | Number Reported | |
|---|---|---|
| | Cases | Deaths |
| Amenorrhea | 36 | |
| Other menstrual disorders | 79 | |
| Breast disorders | 37 | |
| Weight gain | 118 | |
| Oedema | 46 | |
| Depression | 144 | 1 |
| Headache | 266 | |
| Migraine | 15 | 1 |
| Nausea, vomiting | 67 | |
| Pigmentation | 49 | |
| Change in libido | 127 | |
| Thyroid disorders | 11 | |
| Diabetes, hyperglycaemia | 9 | 1 |
| Porphyria | 2 | 1 |
| Neutropenia, aplastic anaemia, etc. | 16 | 1 |
| Cerebrovascular thrombosis, haemorrhage, etc. | 174 | 33 |
| Hypertension | 66 | 2 |
| Thrombophlebitis | 595 | 30 |
| Pulmonary embolism | 355 | 96 |
| Coronary thrombosis | 76 | 46 |
| Other thrombosis | 39 | 5 |
| Other heart disorders | 78 | 7 |
| Other vascular disorders | 43 | 1 |
| Periarteritis nodosa | 1 | 1 |
| Jaundice | 75 | 4 |
| Skin disorders | 145 | 1 |
| Hair disorders | 44 | |
| Tumours | 16 | |
| Other | 550 | 6 |
| Foetal abnormality | 23 | |
| Abortion | 3 | |
| Pregnancy | 21 | |
| All reactions | 3,326 | 237 |
| Persons affected† | 2,864 | 194 |

* Including a few reactions to oestrogens (other than stilboestrol) given alone for other purposes.

† Two or more reactions in some persons—for example, a death in association with both migraine and cerebral thrombosis.

## Three Studies

Evidence that the use of oral contraceptives increases the risk of some types of thromboembolic disorder threefold to sevenfold has now been obtained by three groups of investigators using retrospective methods of inquiry. In one study, organized by the Royal College of General Practitioners (1967), doctors interviewed young women who were recorded in the diagnostic index as having attended for a new episode of vascular disease. In another study Vessey and I (Vessey and Doll, 1968) investigated young women who had been admitted to one or other of the large general hospitals in the North-west Metropolitan Hospital Region for pulmonary embolism, or venous, cerebral, or coronary thrombosis, and who had no previous predisposing cause for the disease. In the third study Inman and Vessey (1968) investigated, on behalf of the Committee on Safety of Drugs, all the deaths that had occurred in England, Wales, and Northern Ireland during 1966 in women aged 20 to 44 years in which thrombosis or embolism of the pulmonary, cerebral, or coronary vessels was referred to on the death certificate. For control purposes, similar information was sought by a similar method in each of the three studies from a group of other women selected according to specified rules to match the affected patients with regard to age, parity, marital status, and, where appropriate, such other factors as the absence of conditions that predispose to the development of thromboembolism.

The general practitioners' study was mainly concerned with superficial phlebitis, and the results showed that the risk of developing it was about three times as great for women who were using oral contraceptives as for those who were not. The results of the other two studies are summarized in Table IV. When other predisposing causes are absent, the risk of devel-

TABLE IV.—*Use of Oral Contraceptives in Women Suffering from "Idiopathic" Thromboembolic Disorders (Expected Numbers in Parentheses)*

| Disorder | Source of Data | No. of Affected Women with a History of Oral Contraceptives | | No. Studied | | Relative Risk: Users to Non-users |
|---|---|---|---|---|---|---|
| | | Used | Not Used | Affected Women | Control Women | |
| Deep-vein thrombosis or pulmonary embolism | Inpatients | 26 (5·0) | 32 (53·0) | 58 | 116 | 8·6 to 1 |
| | Deaths | 16 (4·2) | 10 (21·8) | 26 | 998 | 8·3 to 1 |
| Cerebral thrombosis | Inpatients | 5 (1·0) | 4 (8·0) | 9 | * | 10·0 to 1 |
| | Deaths | 5 (1·5) | 5 (8·5) | 10 | * | 5·7 to 1 |
| Coronary thrombosis | Inpatients | 0 ( 0·7) | 13 (12·3) | 13 | * | — |
| | Deaths | 18 (11·4) | 66 (72·6) | 84 | * | 1·7 to 1 |

* As in the corresponding control groups for women with deep vein thrombosis or pulmonary embolism.

oping deep vein thrombosis, pulmonary embolism, or cerebral thrombosis is increased by the use of oral contraceptives about eight times, while the risk of developing coronary thrombosis is apparently unaltered. In the case of cerebral thrombosis the numbers are small, but, even so, the differences are statistically significant; moreover, they are supported by several impressive but uncontrolled clinical series—for example, Illis, Kocen, McDonald, and Mondkar (1965), and Bergeron and Wood (1969).

The evidence to justify the conclusion that these results indicate a cause and effect relationship has been reviewed elsewhere (Doll and Vessey, 1969), but two points may be considered as they have some bearing on the recognition of unwanted drug effects in general.

Firstly, there is no evidence that doctors have admitted patients to hospital with deep vein thrombosis or pulmonary embolism more readily when they were using oral contraceptives than when they were not. In the hospitals we studied the quarterly number of admissions for these conditions among women who were using oral contraceptives increased pari passu with the increase in the use of oral contraceptives in the general population, and there was no appreciable increase in the admission rate following periods of maximum publicity of the adverse effects of the drugs. Moreover, the proportion of patients who were using oral contraceptives increased progressively from 25% when the diagnosis was uncertain to 75% when it was firmly established. Had there been a tendency to admit patients more easily when they were on contraceptives the trend should have been in the reverse direction.

Secondly, Vessey and Weatherall (1968) have shown that the trend in the national death rate for pulmonary embolism is compatible with the increase in the use of oral contraceptives and the estimates of the associated risk with them. For men in most age groups the trend in mortality continues to be the same as it was before 1960, when the contraceptives were introduced. For women, however, the rate of increase has been greater since 1960 in young age groups but not in older age groups, and the excess mortality is about what would have been expected in the light of the estimated risks.

Quantitatively the results imply that the mortality from thromboembolic disorders attributable to the use of oral contraceptives is about 2 per 100,000 women per year, and adds about 2% to the total mortality normally experienced by women of the relevant ages.

Other risks also exist, but they have not yet been quantified in the same way. Some women develop hypertension and some develop jaundice, particularly if they have previously developed jaundice in pregnancy or suffer from the Dubin–Johnson syndrome. Some show reduced tolerance of carbohydrates, and a few develop porphyria. These effects have been recognized by acute clinical observation or have been predicted from theoretical considerations. They have been confirmed by laboratory studies, or by showing that the effect can be made to disappear when the agent is withdrawn and to recur when it is administered again.

## Enteric-coated Potassium Chloride

I would like now to consider two other reactions that have not been commented on by the committee, but which illustrate special difficulties in recognition. In 1958 the pharmaceutical industry introduced tablets of thiazide and potassium chloride that would not dissolve until after they left the stomach. Within three years Dr. H. J. Roberts, a physician in Palm Beach, reported that 11 patients who were taking the combined drugs had complained of severe abdominal distress, including one who suffered massive gastrointestinal bleeding and who had previously taken hydrochlorthiazide alone without trouble (Roberts, 1961). No reference was made to the fact that the tablets were enteric-coated and no further report of their ill effect was published until 1964, when Lindholmer, Nyman, and Räf operated on four cases of stenosing ulcer of the small bowel in one hospital in Stockholm in one month. As a result of this experience Lindholmer and Räf (1965) searched the records of six Stockholm hospitals for cases of small-bowel obstruction in adults since 1954, and, after excluding those due to neoplasms, hernia, regional enteritis, or specific inflammation, found 1,045 spread out evenly over the years. Of these, 997 cases were attributed to bands, adhesions, etc., 14 to stenosis secondary to some other condition, and 34 to primary stenosis, usually in association with a small ulcer. None of the primary cases had been operated on before 1958, but the numbers subsequently increased until 1964, when 10 were diagnosed in the first nine months. All the patients had been taking thiazides, and at least 30 had also been taking potassium chloride.

In 1964, also, Baker, Schrader, and Hitchcock encountered 11 cases of localized small-bowel stenosis and one case of a perforated ileal ulcer during 15 months' surgical practice in one hospital in the United States, and reported that no comparable cases could be found in the hospital records before June 1963. Eleven of the patients had been under treatment with thiazides and potassium chloride before admission, and attention was drawn to the fact that the potassium chloride was given in enteric-coated tablets.

No cases in association with drugs were recorded in Britain until 1965, when Binns, Pittman, Burley, and O'Brien sent a questionary to 98 doctors holding appropriate hospital appointments. Eighty-two replied, but only two cases were known, both of which had occurred in the previous year. When Binns (1966) presented these data to a meeting of the European Society for the Study of Drug Toxicity, Räf commented that he would probably have obtained an equally unimpressive result if he had simply questioned the heads of the surgical clinics in Stockholm. A few months later Ashby, Humphreys, and Smith (1965) reported the occurrence of seven cases in three British hospitals in two years—all in association with the use of enteric-coated potassium chloride and thiazide tablets—and it seems probable that Räf was right in suggesting that circulation of a questionary was an inadequate method of case-finding.

Many more cases were reported in the next two years (see Wayte and Helwig, 1968), and when it was also shown that high concentrations of potassium chloride could produce ulceration of the small bowel in dogs and monkeys (Boley *et al.*, 1965; Davies and Reinert, 1966) the manufacturers withdrew the tablets and the epidemic ceased.

Non-specific ulceration of the small bowel, like phocomelia, had always been with us (Watson, 1963). Its incidence, however, was increased enormously by the use of a drug, and the only difficulty in recognizing the connexion was in thinking of the possibility. Altogether 14 cases of perforation or obstruction of the small bowel were reported to the Committee on Safety of Drugs, all in association with the use of potassium chloride, but the first case was not reported until 1965, after an editorial on the subject in the *British Medical Journal* (1964b).

## Carcinogenic Hazards

My final example is the induction of cancer—a risk that has been considered with many drugs so that tests of carcinogenicity in experimental animals are now included as part of the routine investigation of a new product. In fact, few drugs have ever been shown to be carcinogenic to man, the principal exceptions being arsenic (which has never been shown to be carcinogenic in animals), Thorotrast and other radioactive substances, coal-tar ointments, oestrogens when given to males, and chlornaphazine—a substance used in the treatment of myelomatosis—which is metabolized to β-naphthylamine and which prolonged life sufficiently to permit the development of

tumours of the bladder. To these may perhaps be added liquid paraffin in the days before polycyclic hydrocarbons were removed from it (see for review Doll, 1967 ; Chassagne, 1967).

Most of these effects were recognized because the incidence of cancer was so high (five of the eight patients given more than 175 g. of chlornaphazine developed bladder tumours) or because of some pathognomonic characteristics (the histological appearance for the Thorotrast cancers of the liver and the site and accompanying pigmentation for the arsenical cancers of the hand). The cancers of the bowel associated with the use of liquid paraffin, however, were recognized only as the result of a large-scale retrospective study of hundreds of patients.

The suggestion that isoniazid might be carcinogenic raised a difficult problem that is likely to be typical of others in the future. Juhász, Baló, and Kendrey (1957) gave 82 mg. to each of 50 white mice in daily injections spread over a month, and found that lung adenomas and leukaemia each developed in seven animals, whereas no tumours developed in 50 control animals. Their results were confirmed by several other investigators (see Juhász, 1967), and there is no reason to doubt that isoniazid—probably as a result of the hydrazine group—is carcinogenic in several strains of mice. The difficulty in investigating its effect in man lies partly in the fact that cancers (other than leukaemia) are unlikely to appear less than 10 years after exposure, and any cancers that might be produced would not be distinguishable from those that occurred from other causes. And in this case there is the added difficulty that repeated *x*-ray exposure and tuberculosis itself may increase the cancer incidence in patients irrespective of the treatment. Only Hammond, Selikoff, and Robitzek (1967) have as yet recorded any relevant observations. They studied 311 men who had been treated with isoniazid between 1951 and 1956 and 644 children whose mothers had been treated with isoniazid while pregnant and found no evidence of any appreciable cancer risk. The duration of observation was, however, short, and the possibility of a risk—unlikely though it is—has not been finally excluded.

No solution has yet been found to the problem of extrapolating to man the results of experiments in carcinogenesis in animals. Certainly there is no justification for prohibiting what might be a useful drug on the basis of the production of cancer in one species of animals by irrelevantly large doses given by a different route to the one that would be used. But this is an extreme case. In practice there are likely to be many situations in which new drugs will have to be introduced and old drugs will continue to be used despite the fact that they can cause cancer in special circumstances ; special studies will have to be undertaken to see whether there is any risk to man, and, if there is, to assess its size.

## Methods of Detection

It appears, therefore, that no single method of investigation could enable all unwanted effects to be recognized and avoided with the minimum of delay. Several methods need to be used to meet the different problems posed by different drugs.

### Pharmacological Experience

Firstly, pharmacological experience and knowledge of the mechanisms by which drugs act should enable many of the effects to be predicted, the therapeutic effects to be retained, and the unwanted effects to be avoided. An increased research programme devoted to the mechanisms of drug action in man is, as Sjöqvist (1965) says, "an excellent method to safeguard pharmacotherapy, far superior to . . . the withdrawal of useful drugs from the market." The continued development of experimental pharmacology in animal laboratories, however, is not enough. Under the aegis of the pharmaceutical industry it has already outrun the facilities for characterizing drug action in man and for the assessment of therapeutic efficacy. The introduction of potent drugs into medical practice demands a close association between basic pharmacology and clinical medicine. More university departments of clinical pharmacology are needed, and existing departments need more support and a higher status within the hierarchy of the medical school.

### System of Medical Intelligence

Secondly, we need an efficient system of medical intelligence. Mortality statistics have provided an important source of information about trends in the public health in the past, and the information gained from the trends in mortality from asthma and from pulmonary embolism shows that they still have a place in the new field of drug monitoring. Their role could be even more important if medical students were encouraged to improve the accuracy of death certification, instead of being discouraged (as they sometimes are) by being told that it is too inaccurate for any serious scientific purpose. Morbidity data would be even more valuable. We need, and could have, hospital admission rates by cause. But we need these for persons and not, as provided by hospital activity analysis, for total admissions irrespective of the number of people affected. Trends in hospital admission rates should warn of epidemics of rare conditions, such as non-specific ulceration of the small bowel, which might otherwise fail to be noticed. We need also to extend the present system for the notification of congenital malformations to enable individual patients to be identified for research purposes, so that retrospective studies can be undertaken of the factors to which they have been exposed.

### System of Record Linkage

Thirdly, we need a system of record linkage embracing registration of birth and death and the records collected within the Health Service. Proposals for a system of this type were first put forward by Acheson, Truelove, and Witts (1961) and have been developed by the Medical Research Council (1967) and the Society for Social Medicine (1968). They are now partly being put into effect in Scotland and Northern Ireland. Such a system cannot immediately replace other methods of drug monitoring in Britain because of the difficulty in identifying the patients to whom prescriptions are given and in handling the immense amount of data that would be produced. It would, however, be of the greatest value in facilitating the follow-up of groups of patients exposed to specific drugs, in recognizing links between diseases—one of which may be brought about by the treatment of the other—and in looking for cancer risks which require the examination of data collected at widely different points in time.

We may note, however, that more complex schemes that aim to provide complete monitoring are being developed in the United States and Sweden. In San Francisco, for example, all the prescriptions given to 125,000 members of the Permanente Insurance Scheme that are dispensed in the hospital pharmacies—that is, 80 to 85% of the total—are coded in a form suitable for computer analysis, and all diagnoses, whether made in hospital, in the doctor's consulting-room, or in the patient's home, are linked to them. In this case linkage is made easy by the fact that no one can make use of his right to health insurance without presenting a card showing his identifying number (Collen, personal communication). If these systems can be extended to cover larger populations and methods worked out for analysing the relevant data, the maintenance of other less complete methods of monitoring in other countries may prove redundant.

### Controlled Observation

Fourthly, we should make further efforts to discover unsuspected effects before the drug is released for general use. No one is better placed to detect an effect than the experts who are trusted with the initial trials of the drug, and we need to make the best use of the opportunity for controlled observations that these trials present. It is difficult to lay down hard-and-fast limits to the number of patients that should be treated in this way, as the number available may be small. If, however, we can obtain for this purpose the sort of medical co-operation that Marc Daniels achieved in the treatment of tuberculosis we could often hope to have observations on some 500 patients, before the drug was released for general use—and without causing undesirable delay.

### Early Warning System

Finally, we need to continue with an early warning system similar to, but not I think identical with, the one we have at present. The special object of such a system is to pick up those effects that are so rare that individual investigators cannot be expected to recognize them. The submission of reports on a national scale should therefore be requested only for those effects that are unusual or severe and unexpected in the light of existing knowledge of the effects of the treatment or of the natural history of the disease. Exclusion of reports of all reactions to new drugs "no matter how trivial" would relieve the individual doctor of the burden of frequently reporting effects that cannot be effectively analysed and would enable the committee's staff to devote more of their time to the detailed investigation of potentially important reactions. Such reports are of value even with the present limited system for assessing the number of people who have been exposed to the drug when the effect is specific to the drug or its incidence is increased so greatly that an excess can be recognized from the crude estimates of incidence based on sales data and grossly incomplete reporting. They are also of value when the reports are made before any question of a risk has been raised in the medical press, so that unbiased comparisons can be made between the proportions of different effects reported with different drugs. In other circumstances, however, any conclusions may be misleading.

Incomplete reporting may lead to the conclusion that a real risk is absent and the selective reporting of suspected risks may give a false impression of a risk that does not exist—as, I suspect, happened after it was suggested that the use of meclozine and other antihistamines for treatment of nausea of pregnancy produced malformations in the foetus. The collection of voluntary reports needs, therefore, to be supported by an epidemiological technique that enables a reliable estimate to be made of the incidence of the reported effect. The most attractive method is to use the practitioner's prescription as the source of information about the patients at risk, because it already includes a code number for the doctor; and the drug and the amount prescribed have to be coded by the Ministry's Pricing Bureau. Its defect is that the patient's age is not recorded and his name and address are often illegible. It might be possible, however, to get 1,000 general practitioners to write the name and address clearly and to insert the age—perhaps with the encouragement of an additional fee.

If, then, all new drugs and selected old drugs were maintained on a special list until such time as experience had shown that they were free from serious side-effects, all that would be needed would be for the Pricing Bureau to put aside for future analysis (instead of destroying) the relevant prescriptions authorized by the sample of practitioners. The frequency of major reactions in these patients could then be determined, if and when required, by personal inquiry or by checking against hospital discharges. A limited scheme of this sort has been possible in Northern Ireland, and Professor Wade (1968) has used it to show that the suspicion that long-acting sulphonamides might cause deformity of the foetus was unfounded. Alternatively, the pharmacist might be asked to ensure that the patient's identity was recorded legibly for all prescriptions for a short list of drugs; this could be kept short by allocating, say, one in twenty of the drugs on the list to each pharmacy. Such methods should be adequate for determining the incidence of a condition like jaundice.

For less obvious reactions like the headaches that followed the use of tranylcypromine we would need to rely on intensive monitoring in selected hospitals. This cannot be undertaken, however, without reorganizing the methods for recording drug prescriptions and the occurrence of unwanted effects, nor without involving clinical pharmacologists in the day-to-day work of the hospital. When this is done the possibilities are great, as has been shown by Wade in Belfast (Hurwitz and Wade, 1969), Crooks in Aberdeen (Coull, Marron, Weir, and Crooks, 1968), Seidl in Baltimore (Seidl, Thornton, Smith, and Cluff, 1966), and Jick in Boston (Slone *et al.*, 1966; Jick, Slone, Borda, and Shapiro, 1968).

If, in these conclusions, I have stressed the part to be played by the development of clinical pharmacology and improved record keeping and communication within the profession made possible by the development of computers, this is because the relative importance of these methods is likely to increase. The burden of responsibility, however, will remain for many years on the shoulders of the physicians who first use new drugs in clinical practice, and new discoveries will continue to owe their origin to people like Mr. Rowe, who noticed that his wife's migraine came on after a meal of cheese; Dr. Blackwell, whose mind was receptive to a new idea; and Drs. Corner and Greenberg, who were worried by the unexpected death of a few asthmatics.

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# Treatment of Acne Vulgaris with Tetracycline Hydrochloride: a Double-blind Trial with 51 Patients

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**Summary: Fifty-one patients with acne vulgaris were included in a double-blind trial to assess the therapeutic effect of 250 mg. tetracycline hydrochloride twice daily for three months. The results, assessed clinically and photographically, showed that tetracycline hydrochloride had a statistically significant beneficial effect. Hence, since it is cheap and rarely has side-effects in healthy young adults, its use is suggested, as well as local therapy, in the more severe forms of acne.**

## Introduction

Tetracyclines have been used in the treatment of acne vulgaris for over 15 years and yet their value is still uncertain. The results of double-blind trials are conflicting—for example, Stewart *et al.* (1963), Witkowski and Simons (1966), and Ashurst (1968) confirm their value, while Smith *et al.* (1962), Crounse (1965), and Fry and Ramsay (1966) are of the opinion that tetracyclines have no greater effect than a placebo (*Year Book of Dermatology, 1966–7*).

The *British Medical Journal* (1966) was critical of the long-term use of tetracyclines and emphasized the expense and the many possible side-effects. It was because of this continued controversy that we undertook yet a further trial with a tetracycline to see if it produced a significant effect in this condition.

The therapeutic results of more than one type of tetracycline, or of other broad-spectrum antibiotics, are not considered here. The questions of total duration of treatment and of possible relapse of acne after stopping tetracycline therapy are also beyond the scope of this paper.

## Investigation

Sixty-one consecutive patients with acne vulgaris attending the skin department of the General Infirmary at Leeds were included initially in the trial. Five failed to attend after the first visit and five others attended twice only. The figures for this trial are based on the 51 patients who attended three times over a period of three months.

There were 25 females aged 12 to 29 years (mean 18 years) and 26 males aged 14 to 23 years (mean 18 years). None of the patients included in the trial had been treated with antibiotics within the previous two months. Forty-four of them had had local treatment in the past, and four had had superficial *x*-ray therapy over a year previously. The trial was conducted during the winter months (from December 1967 to April 1968), when sunshine was minimal.

At the first attendance a clinical assessment was made by completing a table which included descriptions of the lesions—

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