DRUG SURVEILLANCE:
The Role of the Committee on Safety of Medicines
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It should be emphasised that it is not only new drugs that can give rise to adverse reactions. In a recent survey in Belfast (Hurwitz and Wade, 1969) it was found that 19.8 per cent of patients treated with digoxin suffered adverse reactions to it, and that adverse reactions to digitalis accounted for one third of all drug reactions monitored. Withering in 1785 was aware of the fact that the drug he had pioneered was not without hazard and wrote “it is better the world should derive some instruction, however imperfect from my experience than that the lives of men should be hazarded by its unguarded exhibition, or that medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.”

I. THE NEED FOR DRUG CONTROL AUTHORITIES

(i) The beginning of monitoring of drug hazards

The objective assessment and measurement of the efficacy of drug therapy is a recent discipline. Attempts to measure and assess the ill effects of drug therapy are recent and as yet can hardly be called a discipline. Yet it was in 1877 at a meeting in Manchester that the British Medical Association initiated the first collaborative study of the adverse reactions of a drug. A committee was set up to investigate the sudden unexpected deaths which sometimes occurred during the induction of chloroform anaesthesia (McKendrick Coats & Newman 1880). Since that time there has always been some concern amongst doctors about adverse reactions to drugs; and reactions to smallpox vaccine, typhoid vaccine and more recently poliomyelitis vaccines have been a continual source of anxiety not only to doctors but also to the public, whose fears have sometimes been fanned to great emotional heights by anti-vivisectionists and anti-vaccinationists. At the end of the First World War, an epidemic of jaundice and fatal hepatic necrosis amongst soldiers treated for syphilis with organic arsenicals was so serious that it was the subject of a special report by the Medical Research Committee predecessor of the present Medical Research Council (Medical Research Council, 1922). And a few years later it was recognised that fatal jaundice could be caused by cinchophen, a remedy used in the treatment of gout (Worster-Drought, 1923; Short & Bauer, 1933), and agranulocytosis by the analgesic drug amidopyrine (aminophenazone; aminopyrine; Pyramidon) (Madison & Squier, 1933; Kracke & Parker, 1934).

The introduction of the sulphonamides to medicine in the late 1930’s brought familiarity with adverse reactions to all doctors. But these drugs, penicillin, strepto-
mycin and the corticosteroids led to such advances in the efficacy of medical treatment that the adverse reactions although recognised, caused no great anxiety. This state of affairs was changed in 1961 by the thalidomide catastrophe (Mellin & Katzenstein, 1962). This tragedy left its mark not only on the unfortunate children but also on the medical profession, the pharmaceutical industry, the public and on governments. Now it is recognised that there is an urgent need to determine not only the adverse reactions that a drug may cause but the incidence of those reactions in relation to the use of the drug, and to determine sections of the population at greater than average risk (D'Arcy and Griffin, 1972).

(ii) The Thalidomide disaster

In view of the historic importance in terms of legislation it might well be desirable to spend some time describing the spectrum of thalidomide toxicity.

(a) Thyroid dysfunction

The first adverse reaction reported caused by thalidomide, oddly enough was the least important and that was the development of myxoedema. This report was made in 1959.

(b) Neuropathy

Early in 1960 isolated reports were received by Burley of Distillers Company (Biochemicals) Limited, from various parts of Great Britain describing symptoms and signs suggestive of peripheral neuritis occurring in patients receiving thalidomide regularly for periods of six months or more. Florence, however, recorded the first report in the literature in December 1960. In four patients polyneuritis had developed while they were taking thalidomide, and he thought that the symptoms could possibly be a toxic effect of the drug. Kuenssberg et al soon added five similar cases in January 1961. It was not till the more detailed report of Fullerton and Kremer in September 1961 that the association of thalidomide and resulting neuropathy became fully realised in Great Britain.

(c) Teratogenicity

In December 1959 Weidenbach presented the case history of a girl born on November 10, 1958, to a twenty-four-year-old primigravida. The upper and lower limbs were missing. The hands and feet originated directly from the shoulder and pelvic girdle respectively. There were also deformities of the digits. No additional abnormalities were noted. The infant progressed very well in the nursery and continued to develop in accordance with her age. The history of the gestation yielded nothing unusual. Neither parent could recall a family history of malformation. Although it was recognised that no conclusion regarding the aetiology of the malformation could be drawn it was thought that, owing to the symmetry and involvement of all extremities, a hereditary factor was most likely.

Kosenow and Pfeiffer, at the September 1960 meeting of the German Society of Paediatrics in Kassel, had a scientific exhibit describing two infants with similar malformations and also micromelia, hemangioma of the midline of the face and duodenal stenosis.

In September 1961, Wiedemann presented a paper calling attention to the current
increase in the incidence of hypoplastic and aplastic malformations of the extremi-
ties. Over a period of ten months he had seen thirteen patients. He was aware of
twenty-seven similar cases in his area. Since no hereditary signs appeared in the
histories of any of his thirteen patients he considered an exogenous cause that
must have come into effect around the beginning of 1959. He questioned whether
a drug among the constant flow of new drugs entering the market, might have
been involved.

Pfeiffer and Kosenow presented a paper on the question of exogenous causes of
severe malformations of the extremities to the North Rhein-Westphalia Paediatric
Meeting in Dusseldorf on November 18, 1961. They mentioned thirty-four newborn
infants with defects of the long bones seen at the Children’s Hospital at Muenster
from January 1, 1960 to November 18, 1961. After their presentations Lenz, of
Hamburg, raised the question of thalidomide consumption by the mothers. This
was later reviewed, and it was found that a large number of the mothers involved
had taken thalidomide.

The Fetal Life Study received an inquiry in 1962 concerning the incidence of
phocomelia in relation to a recent increase that had been observed in West
Germany. The Fetal Life Study was established in 1946 in a selected population
at the Columbia-Presbyterian Medical Center as a long-term prospective epidemi-
ologic investigation of human reproduction, to determine the incidence of foetal
deaths, neonatal deaths and congenital malformations and to delineate associated
factors. From more than 10,000 pregnancies prospectively followed in the years
1946 to 1960 and more than 2,000 followed in 1961 the group was unable to find
any causes of phocomelia similar to the pictures appearing in the literature. A
possible explanation of this discrepancy became apparent at a Rhein-Westphalia
paediatric meeting in Dusseldorf, Germany on November 18, 1961. Dr. Lenz of
Hamburg, suggested that this malformation was related to the ingestion early in
pregnancy of the drug thalidomide (alpha-(N-phthalimido)glutarimide).

It was not long, however, before individual case reports began to appear. These
cases also illustrated the problem of retrospective epidemiology. In one situation
the drug had to be retrieved from a former neighbour. In another case, in which
the mother had been included in a hospital-study prospective survey, the fact that
she was given thalidomide was not known by her family doctor. In retrospect
studies two out of three family doctors could not remember whether thalidomide
had been taken.

Several communications indicated that small doses might be devastating. One
patient who was a week overdue for a menstrual period took 50 mg of thalidomide
a day for one week only; her premature baby had phocomelia. In another report
the mother apparently received 100 mg of thalidomide for three nights and 50 mg
for two nights in the second week of pregnancy; the baby was born with phocom-
elia. If the dates in these situations were correct these may illustrate the earliest
stages of pregnancy in which teratogenic effects should be sought in the assessment
of teratogenicity. It is even more worrying that in these cases the drug was exerting
its teratogenic effect in women who did not even know for certain that they were
pregnant.
(iii) The continual appearance of new hazards and new dimensions of adverse reactions

The first confirmed reports of the transplacental transmission of cancer in man by means of a hormone, stilboestrol have recently been published. The evidence provided by this extremely important research and its significance need immediate and careful assessment.

Recently Herbst and Scully (1970) reported seven cases of adenocarcinoma of the vagina in adolescent girls in the New England area during a period of four years. The patients' ages ranged from 15 to 22 years. They had symptoms of irregular vaginal bleeding for up to one year. Five were treated by radical surgery and one by wide excision. All were alive one to four years after operation. The seventh, in whom the disease was too far advanced at surgical exploration, died within six months. The authors were puzzled about the causation of this apparent clustering of cases, as carcinoma of the vagina is uncommon and usually occurs at a much older age.

An eighth case was added in a retrospective study of factors that might have been associated with the appearance of these tumours. Herbst and colleagues (1971) noticed that maternal bleeding when the girl's mother was pregnant with the patient and in previous pregnancies was more common than in a control group. But of greater significance than that was the finding that seven of the eight mothers had been treated with diethylstilboestrol during the first trimester of the material pregnancy, while none of the control group was so treated. A separate study by P. Greenwald and colleagues has now confirmed this association, adding five more cases in which the actual dosage of synthetic oestrogen used has been obtained.

All 13 patients were born between 1946 and 1953, a period when stilboestrol was being given for repeated or threatened abortion. All the mothers who took stilboestrol began treatment in the first two months of pregnancy. They received either a constant dose administered throughout pregnancy or a continually increasing dose given almost to term. The actual dosage varied but followed roughly that suggested by A. W. Smith beginning at 5 mg by mouth during the sixth or seventh week of pregnancy and increasing by 5 mg at two-weekly intervals to the 15th week, when 25 mg daily was being given. The dose then increased by 5 mg at weekly intervals until the 35th week, at which time as much as 125 mg of stilboestrol was being taken by mouth daily.

The original series of seven cases exceeded the number of cases in the entire world literature for a tumour of this type in adolescent girls born before 1945. Indeed, adenocarcinoma of the vagina was thought to have some relationship to vaginal remnants. Moreover, if these neoplasms were the result simply of high-risk pregnancies, this should have become apparent before 1945. It was therefore suspected that exposure to stilboestrol and vagina carcinoma in the offspring might have a cause-and-effect relationship. The suggestion is reinforced by the fact that stilboestrol was used only infrequently in general obstetric practice. Even at the Boston Hospital for Women, where a special high-risk pregnancy clinic was being conducted only about one in twenty-one patients delivered in the wards had received stilboestrol during the five year period 1946 to 1951. Thus when the expectancy of a chance association is less than 5 per cent, the occurrence of
maternal stilboestrol therapy in 12 out of 13 cases of vaginal adenocarcinoma in young women cannot be considered coincidental.

II. BACKGROUND TO DRUG CONTROL IN THE UNITED KINGDOM

The role of the Medicines Act 1968 can probably best be understood against the historical perspective of attempts by the government to control the use of potent pharmacologically active agents in terms of quality and efficiency.

The Gin Acts of the 18th century introduced the concept of control over sales and supply, recognised the necessity of protecting the community and pioneered later efforts to overcome the misuse and abuse of drugs.

The British Pharmacopoeia was first published in the 19th century. Successive editions and addenda up to the present day have produced standards of quality control, which have justly enjoyed international prestige. Unfortunately, there has never been an adequate machinery for the enforcement of these high standards.

The Dangerous Drugs Acts recognised the risks of drug addiction, and introduced the idea of control of manufacture under licence, together with strict recording of sale and supply.

The Pharmacy and Poisons Acts and the introduction of the Poisons Rules, elaborated the theme of control over sale and supply. Though designed primarily to deal with poisons; medicines were later included. The control of poisons and medicines by similar rules has been cumbersome and fraught with difficulties, but it has helped to maintain some control in a long process of transition.

The Therapeutic Substances Acts added new concepts to control. The design was the control of substances such as vaccines or sera, the purity and potency of which could not be controlled by chemical means. Such control was difficult to contain within a pharmacopoeial monograph, for it demanded the use of biological standardisation, requiring standard materials, against which the products could be assayed. Many of these standard materials are now international.

The Therapeutic Substances Acts (T.S.A.) further recognised that the personnel and the conditions of the premises in which such products were manufactured were as important in control as the tests which could be applied to the end-product. Thus factory inspection and in-process control played an integral part in the considerations for the issue of a licence under the Acts and their regulations, either to manufacture or to import. For the first time primary considerations of safety began to emerge for these Acts envisaged not only the purity and potency of preparations, but allowed the restriction by prescription to any medicines, which would be a hazard to the community if freely available.

The Cancer and Veneral Diseases Acts were enacted to prevent the public advertisement and promotion of medicines for these serious conditions, thus preventing not only fraudulent claims but protecting the sufferers from inadequate and unsuitable treatment. In this way the control of advertisement and promotional literature for medicines was begun.

It was in this multiplicity of legislation that even before the establishment of the Committee on Safety of Drugs in 1963 that concepts of quality control, restrictions
over sale and supply, of in-process control, and control over promotion and advertisement and of manufacture under licence were born. However, there was considerable complexity of control under the different acts. Although such statutes and regulations as the Pharmacy and Poisons Acts, the Dangerous Drugs Act and the Poisons Rules controlled the sale and supply of some medicines, others came under the control of the Therapeutic Substances Act, and no central agency existed that gave consideration to all medicines, so far as their safety for use in man was concerned. Although everything pointed to the need to consolidate the legislation on medicines, the old machinery seemed to work and for decades no great problem had arisen. The task of preparing consolidating legislation was formidable and disentangling the complex machine was a daunting venture.

Lulled into security by the quiet years, both public and Government were unprepared for the therapeutic explosion of the last thirty years. This complacency was rudely shattered by the thalidomide tragedy. The conscience of the public was troubled and the Government galvanised into activity. No existing legislation was available to take care of this new consideration, and to consider these new concepts of safety and at the same time to produce comprehensive and consolidating legislation was bound to be lengthy and time-consuming. In the meantime, something had to be done, for any product could be marketed, with a few exceptions under the Therapeutic Substances Acts, however dangerous or ill tested it might be. As an interim measure in 1963 the Minister of Health, on advice, established the Committee on Safety of Drugs. The Committee consisted of a panel of independent experts from various fields of Pharmacy, Pathology, etc. and served under the chairmanship of firstly Sir Derrick Dunlop and more recently Professor Scowen. The Committee was serviced by a professional secretariat of pharmacists and medical officers who under took the assessment of the submissions and presented these to the Committee and various sub-committees.

The Committee on Safety of Drugs was set up in June 1963 by the Health Minister, in consultation with the medical and pharmaceutical professions and the British Pharmaceutical Industry, with the following terms of reference: —

(i) “To invite from the manufacturer or other person developing or proposing to market a drug in the United Kingdom any reports they may think fit on the toxicity tests carried out on it; to consider whether any further tests should be made and whether the drug should be submitted to clinical trials; and to convey their advice to those who submitted reports.

(ii) To obtain reports of clinical trials of drugs submitted thereto.

(iii) Taking into account the safety and efficacy of each drug, and the purposes for which it is to be used, to consider whether it may be released for marketing, with or without precautions or restrictions on its use; and to convey their advice to those who submitted reports.

(iv) To give to manufacturers and others concerned any general advice they may think fit.

(v) To assemble and assess reports about adverse effects of drugs in use and prepare information thereon which may be brought to the notice of doctors and others concerned.

(vi) To advise the appointing Ministers on any of the above matters.”

The Committee had no legal powers, but worked with the voluntary agreement of the Association of British Pharmaceutical Industry and the Proprietary Association of Great Britain. They promised that none of their members would put on
clinical trial or release for marketing a new drug against the advice of the Committee, whose advice they would always seek.

An effective drug control authority should have adequate machinery for assessment in three broad functional areas:

(i) scrutiny before clinical trial
(ii) scrutiny before marketing
(iii) surveillance of each drug after marketing so that adverse reactions can be adequately monitored and documented, and if necessary a warning issued to the medical profession.

A strong sub-committee structure was set up, drawing in a wide variety of expertise, which could not be contained within a single committee of workable size. Sub-committees were first formed to advise on toxicity and clinical trials, and in adverse reactions. Later it became necessary to form an advisory group of experts on vaccines and biochemicals.

When an application from a manufacturer was received it could largely be classified into a reformulation or Minor Submission, and a New Drug or Major Submission. These submissions were requesting either permission to market or to conduct clinical trials. The submission was assessed by a pharmacist and then by a senior medical officer of the professional secretariat. A summary was prepared and the submission and summary circulated to members of the appropriate sub-committee before the sub-committee meetings where the data was presented by the Senior Medical Officer dealing with the submission and this was discussed and recommendations were then passed from the sub-committee to the main committee, after which a decision was made and the manufacturer informed.

Clinical Trial

Before clinical trial can be considered full information is required on the chemistry, pharmacodynamics, metabolism, acute and intermediate toxicity, on teratology and in drug interactions. If the pharmacodynamic studies indicate a therapeutic potential and the committee is satisfied with the quality and safety of the drug, no objection is raised to clinical trial. The nature of the trial is the responsibility of the applicant, provided always that the committee can be satisfied that the staff responsible for the trial and facilities available to them are appropriate.

Although a pamphlet, "Notes for the guidance of manufacturers and other persons developing or proposing to market a drug in the United Kingdom" was available, the Committee did not lay down rigid requirements for the pre-clinical toxicity testing programme of new drugs. This was the responsibility of the manufacturer, although the Committee's staff were always available for consultation on the proposals.

The pharmacodynamic properties and therapeutic potential of the new drug are studied and considered in relationship to its metabolism, the pattern of toxicity and its teratogenic potential. Ideally the toxicological and teratological studies should be performed in species that are known to metabolise the drug in the same way as man. Unfortunately, this information on the metabolism is seldom available at this stage and toxicity testing is most frequently performed in the rat and dog and teratogenicity studies on the rat and rabbit. Both toxicological testing
and teratogenicity studies should be performed at three dose levels by the intended route or routes of administration of the new drug. In the toxicological studies the doses should be so adjusted that the low dose is within the range of the proposed therapeutic dose, the high dose so designed that the toxicity of the drug is manifested and the target organ identified. Intermediate term toxicity studies, defined as studies involving less than half the animal’s life-span, are required for two or more species, most commonly the rat and the dog. Detailed haematological and clinical chemistry monitoring is regarded as a pre-requisite of modern toxicology, as are detailed terminal histopathological studies of major organs. If the toxicity tests indicate that one particular organ shows signs of dysfunction, the clinical monitoring of the subsequent trial should involve intensive monitoring of that particular organ, and assurances should be sought that clinical investigation will proceed cautiously. If organ enlargement is a feature of the toxicity studies, histopathological work should be undertaken to find out whether this is a functional hypertrophy or a manifestation of toxicity.

The general recommendations for teratological studies are modest, involving administration of the test drug, during the period of organogenesis, at three dose-levels to two species, usually the rabbit and rat. Evidence should be presented that the strain of animal used produces abnormal offspring following the administration of a known teratogen such as thalidomide. Other investigations such as fertility studies are conducted at the discretion of the applicant.

**Marketing**

When clinical trials have been completed and a request is received for marketing, the assessment will be based largely on the clinical documentation in relation to the proposed clinical use. In the early clinical studies evidence will have been obtained on the absorption, distribution, metabolism and excretion of the drug. In addition, the clinical pharmacology will have been studied, when appropriate.

The preparations of the drug proposed for marketing must show an adequate stability and uniformity of content. It must be clearly demonstrated that methods of formulation and preparation do not modify the drug action or interfere with its biological availability.

Evidence will be sought in the documentation for any sign of possible organ toxicity which might be revealed from the monitoring by haematological and clinical chemical methods. Problems of possible interactions with other drugs must also be scrutinised. In addition at this stage if the drug is intended for prolonged use additional studies will be required of long-term toxicity in animals.

Finally, the proposed promotional literature is examined to ensure that in the view of the committee no extravagant or misleading claims are made and that the necessary precautions and contra-indications are adequately expressed.

**Adverse Reaction Reporting**

The surveillance of drugs after marketing is directed by the Sub-Committee on Adverse Reactions. The primary mechanism for monitoring is based on a voluntary and spontaneous reporting system, using a simple, reply-paid ‘yellow-card’ whereby doctors and dentists are encouraged to report any suspected adverse reactions to
drugs to the Committee. Contact between the Committee and its staff now moved away from the pharmaceutical industry through its medical advisers, to the practising doctor whether in hospital or in general practice. The number of reports of suspected adverse reactions to drugs is a disappointingly low proportion of the total, and the true incidence of even major reactions is as yet not well documented. The fraction reported to the Committee just constitutes the tip of the iceberg, most of which remains submerged beneath the surface of our awareness (Dunlop, 1969).

Collaboration with the World Health Organisation drug monitoring schemes is well established as is also contact with drug regulating authorities in Europe and the F.D.A. in the U.S.A. and Canadian F.D.D.

THE MEDICINES ACT 1968

The Medicines Act of 1968 has resulted in the translation of Committee on Safety of Drugs into the newly formed Committee on Safety of Medicines. An identical sub-committee structure exists but with the addition of a sub-committee on Chemistry, Pharmacy and Standards. Its functions and procedures will differ little from that of its predecessor but it will act as the advisory committee to the Licensing Authority.

The Licensing Authority will issue in effect five major groups of licences:

(a) Licences of Right
   (i) Product Licences—these are applicable to a product already on sale on the duly appointed day, namely 1st September, 1971.
   (ii) Clinical Trials Certificate—applicable to drugs already undergoing clinical trial with the approval of the Committee on Safety of Drugs on the duly appointed day.

(b) Clinical Trial Certificates
    Valid for a period of two years for drugs approved by the Committee on Safety of Medicines for clinical trial.

(c) Product Licence
    Valid for a period of five years on drugs approved for marketing by the Committee on Safety of Medicines.

Under the Medicines Act new provisions are introduced which control manufacture, distribution, and storage of drugs, and to cover these provisions a medicines inspectorate has been established and manufacturers and wholesale dealers have to hold appropriate licences.

(d) Manufacturer's Licence.

(e) Wholesale Dealers' Licence.

The Licensing Authority issue "Notes on Application for Clinical Trial Certificates" and "Notes on Application for Product Licences" as a guide to manufacturers of the nature of the data required. However like the previous Committee on Safety of Drugs no firm recommendations are laid down since the assessment of new drugs is a constantly changing scene in the light of new developments and the awareness of new hazards.

CONCLUSION

"The Committee has thus endeavoured to safeguard the sick by ensuring that new medicines are adequately tested, before they are introduced for trial: by ensuring that the preparations are constant and appropriate before marketing, and that their therapeutic potential outweighs any possible hazards; and that the claims are reasonable, and the precautions outlined. In addition, it maintains
a close surveillance after marketing, so that any unexpected or unusual effects may be recognised at the earliest opportunity and the professions informed of them.

The Committee, however, would be failing in its task of safeguarding the sick, if its attention was totally focussed on aspects of safety alone. For absolute safety cannot exist and the more potent the remedy, the more may be the capacity for harm. This is a difficult road to travel for the sick are not safeguarded if undue restriction and caution impedes therapeutic advance, and constant care is required to ensure that no patient shall be deprived of any potential therapeutic advance even at an early stage of development if an urgent need arises.” (Scowen 1971).

Quite clearly the standard of safety or freedom from toxicity must be greater for a drug which is used for a trivial indication, e.g., a headache than for a drug that is effective in potentially life threatening condition.

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