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the benefits and risks of pharmaceutical innovation

The fifth in a series of
Office of Health Economics monographs
dealing with aspects of the
prescription medicine market in Britain

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Office of Health Economics

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Contents

Foreword

Since this monograph was completed, two new stories concerning the safety of medicines have been featured prominently in the British press. The first has been on an American legal case in which damages have been awarded because a medicine taken during pregnancy was alleged to have caused congenital malformations. The second has been based on the fact that the benzodiazepines, when taken for prolonged periods in high dosage, may carry the risk of causing dependency.

Although this monograph was written too early to discuss either of these allegations each of them highlights the conclusions to be drawn from it.

First, no medicine is free of all risks, although the existence and extent of these risks is often highly debatable. Second, more centrally, these risks need to be seen in perspective against the benefits. For the benzodiazepines in particular, their enormous advantages and safety in comparison to those of earlier alternatives are fully discussed in the monograph and remain unquestionable. Their risks of causing dependence have been officially stated to be small; and any harm which benzodiazepine dependence may cause must be judged not only against the dangers of the barbiturates but also, for example, against the hugely greater risks of dependence and social catastrophe still arising from the excessive consumption of alcohol.

Disproportionate emphasis on the risks of medicines can itself be extremely harmful. It can not only deny their own specific benefits to patients in need; more importantly it can slow down the whole pace of therapeutic progress.

Thirdly, these two new stories emphasise the importance of taking all possible steps to minimise the risk from the use of medicines. The monograph discusses the measures which have already been taken in this connection and those which are at present under discussion.

Here, cost as well as administrative complexities have to be set against whatever real benefits can be expected in terms of safety. There are no easy answers, despite the often simplistic terms in which such problems are discussed.

Finally, every new pharmaceutical 'scare' story underlines the importance of careful prescribing. The monograph describes the evidence that doctors have become considerably more cautious in their adoption of new medicines since the original thalidomide tragedy. Nevertheless, careful prescribing must not be equated to therapeutic nihilism. Once again the enormous benefits of medication which are described in this booklet have to be remembered.

All in all, these two recent allegations of the dangers of medicines in no way detract from the conclusions of this monograph They serve to underline the fact that the assessment of the benefits and risks of medicines is essentially a question of balance – and if we are not careful that balance is in serious danger of being swung too far against the development of those future new medicines which are needed to extend the dramatic therapeutic progress which has already been achieved in the past 30 years.

Introduction

The multinational pharmaceutical industry is currently spending well over £2,500 million a year in research and development. There is a danger that the basis of this huge investment and the successful therapeutic progress resulting from it could be jeopardised by the irrational attitudes which are developing to the risks associated with the prescribing and taking of new medicines. This paper examines this problem and attempts to set into perspective the hazards of medication when seen against the enormous benefits which have been derived from it. The paper starts first with a brief discussion of the background to risk assessment. Next it catalogues some of the major benefits which have been achieved with new medicines over the past 30 years. It goes on to examine the actual hazards which have been associated with this progress. It then describes the measures which have been taken to minimise these risks. Finally, it sums up the issues involved.

Background

The major problem of public ambivalence towards benefits and risks is, of course, by no means confined to medicines and is no new phenomenon. The irrationality of risk assessment was well described by Chauncey Starr in the United States in 1968.[1] It is typified by the contrasting attitudes to travel safety and to nuclear power. In Britain about 7,000,000 people have been injured on the roads in the past 20 years. Road accidents currently kill over 6,000 people a year. Despite all the government attempts to reduce these casualties, there will still remain a substantial number which will be accepted as an inevitable price to be paid for the modern necessity of road transport. Again, air travel has a high safety record but it is not free from real risk. By contrast, the risks associated with the use of nuclear energy to generate electricity remain largely theoretical. Yet these theoretical risks, accentuated by the enormous publicity given to a number of non-fatal nuclear accidents, have greatly delayed the introduction of nuclear power stations, particularly in Britain. Against this background it is not surprising that risks in the medical field are also viewed irrationally. But here a sense of perspective is particularly important, and difficult to achieve. Doing nothing for a seriously ill patient usually involves the greatest risk of all. However, if death results from such 'masterly inactivity' it is ascribed to natural causes and no further consideration is given to the matter. Equally, the relative risks of surgery and medication are seen badly out of balance. Bunker has estimated that surgery in Britain is associated with 20,000–30,000 deaths per year.[2] He points out that this is ten times the number of deaths which official statistics attribute to medicines – and the vast majority of these result from deliberate or accidental over-dosage. Yet the risks of surgery are taken for granted, while those associated with medication regularly receive critical attention.

The existence of medical risks is, of course, no new problem. Since the earliest days, medical and surgical treatments have been associated with adverse effects. Indeed, until the scientific advances of this century, most treatments were ineffective and were often hazardous. This was true not only for many forms of surgery, but also for some of the routine medical treatments – such as purging and bleeding – used even for relatively minor disorders. A fallacy current over the past decade has been to think that the dramatic therapeutic advances of the second half of the twentieth century could have been achieved without some continuing risk and without paying the price for progress represented by occasional serious mishaps such as the thalidomide disaster in the early 1960s. This is an aspect of the general fallacy that technology can assure perfect safety. In the case of pharmaceutical innovation it has led to unduly critical attitudes on the part of many people towards the adverse reactions resulting from modern medication. While it has been pointed out that surgical risks still seem generally to be accepted, unfortunate experiences with vaccines and with recently introduced medicines have led to severe and often irrational attacks on them because of their harmful effects. However, before looking to the recent past and to the present, it is worth re-emphasising some of the pharmaceutical hazards which were uncritically accepted until the last few decades. First, in anaesthesia many people discounted the risks associated with the use of chloroform and ether. As recently as the 1950s some anaesthetists still advocated the 'open mask' method of administering chloroform, drip by drip, as the operator made a subjective assessment of the depth of anaesthesia being induced. More alarmingly, since chloroform could with some justification be claimed as a surprisingly 'safe' agent, anaesthetists, dentists, obstetricians, chest physicians and others were at the same time still using the local anaesthetic amethocaine. This could kill suddenly and often unpredictably (although its mortality could be reduced by previous skin testing for hypersensitivity) and these deaths often occurred in healthy children and adults undergoing minor surgery. Its overall mortality, even in relatively careful hands, was of the order of one death per 5,000 patients. More dramatically the 27th Edition of Martindale's *Extra Pharmacopoeia* in 1977 quoted the following statement in its section on the toxic effects of amethocaine: 'The incidence of hypotension within 15 minutes of the induction of spinal anaesthesia was reduced to 11 per cent and mortality within the first 10 days after operation to 6 per cent in 200 patients, mostly elderly, when anaesthesia was induced with amethocaine with the patient in the supine position with the head slightly lowered: the incidence of hypotension in a similar group of 200 patients had been 35.5 per cent and mortality 13 per cent when anaesthesia was induced in the lateral position.'[3]

1 Social Benefit versus Technological Risk; *Science*; Vol 105, pp 1232–38.

2 Bunker J. In Benefits and Risks in Medical Care; ed Taylor D J, OHE (1974).

3 Quoting Winnie A P. *Journal of the American Medical Association* 207 1663; see also criticism, Root E B. *ibid* 208 1192; (1969).

The benefits

This six per cent mortality, reported as late as 1969 – and presumably partly caused by the anaesthetic – is a sombre reminder of the risks which were still so recently accepted for older pharmacological compounds.

Similarly, the use of the toxic mercury salts, of arsenic, of the arsenical compounds and of strychnine was only gradually discontinued during the middle part of the twentieth century when new, safer and more specific remedies emerged from the modern research laboratories. As a last example, which will be referred to again later, it is worth remembering that the amphetamines were not only in general use but were on free sale to the public without prescription as late as the 1950s. These compounds, which are now regarded as too addictive even for prescription, were widely used for social purposes, such as 'premedication' for a student's examination session after a late night out at a party, or for the treatment of obesity. At the same time, barbiturates were used indiscriminately as standard hypnotics, particularly for hospital patients, regardless of the risks which are now known to arise from their routine use. The present undue concern about adverse effects of modern medicines needs to be judged against the public attitudes which still regarded many of these historical risks as acceptable only twenty years ago. One problem, of course, is that such therapeutic hazards may sometimes only appear in retrospect. This factor probably contributes substantially to current excessive fears of medication.

Apart from the contrast with these hazards of medications used in the past, current known and possibly unknown risks need to be judged in perspective against the benefits obtained. Of course, much of the reduction in mortality and morbidity during the twentieth century has been part of a long-term trend in the improvement in health due to better nutrition, better housing and sanitation and a reduction in poverty and squalor generally. However, those who argue that modern medical progress has contributed little or nothing by comparison seriously overstate their case. As this section of the paper will record, there have been very many specific and dramatic improvements in health status due entirely to modern pharmacological progress.

The first, and universally accepted example, is with tuberculosis. Mortality from this cause in Britain had already been declining during the latter part of the nineteenth century to an annual rate of about 150 deaths per 100,000 by 1900. After that, with the exception of the two World Wars, mortality continued to decline until the mid-1940s, when it accounted for 50 deaths per 100,000. However, there were still long waiting-lists for the crowded tuberculosis sanatoria with over 30,000 beds occupied by tuberculous patients.

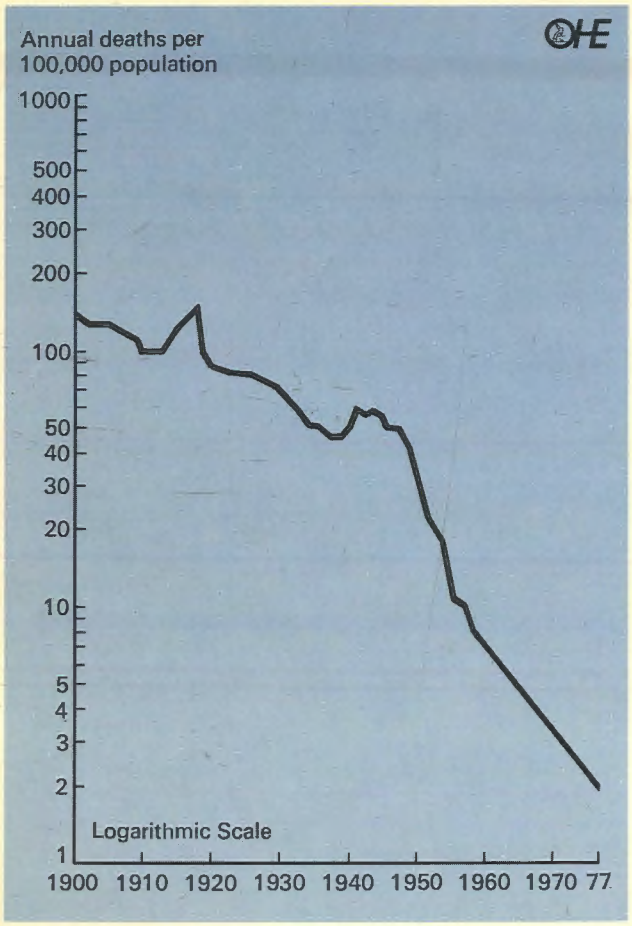
At that point, with the introduction of streptomycin, isoniazid and para-aminobenzoic acid, there was a sharp change in trend in the fall in mortality (Figure 1). By 1976 the death rate had fallen to about 2 per 100,000. Not only that, the most dramatic fall had been among children and young adults. In the age group up to 29 years, there had been over 8,000 deaths in 1945; in 1977 there were 14. The over-crowded sanatoria emptied rapidly from the late 1940s onwards.[4]

A second equally dramatic example of progress came in the treatment and control of the other childhood infections. Figure 2 shows the reduction in deaths due to diphtheria following the introduction of vaccination at the beginning of the Second World War. In this case it is ironic that the vaccine had been available throughout the 1930s, but the traditional caution of the medical profession had delayed its general use in Britain until the crisis of wartime.[5] Pneumonia and meningitis were two more infections where the fall in mortality was accelerated by the introduction of the sulphonamides and antibiotics in the 1930s and 1940s. Similarly,

4 There are still about 2,000 beds occupied by tuberculosis patients. However, many experts consider that most of these patients are now in hospital unnecessarily.

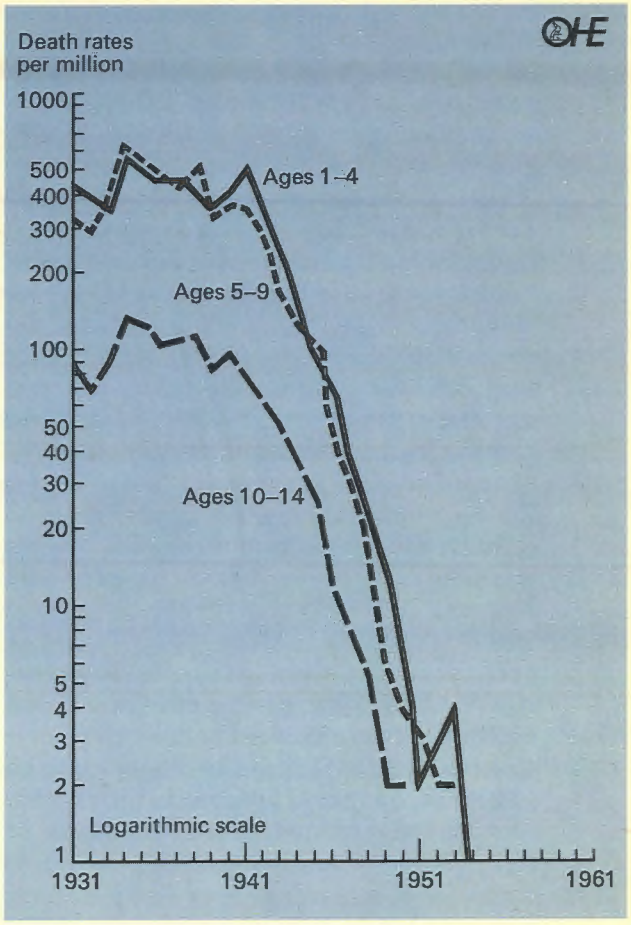
5 Diphtheria had been virtually eliminated in Canada in the 1930s by a programme of immunisation there.

1 **Mortality rate from tuberculosis. England and Wales 1900–1977**



Source DHSS

2 **Diphtheria. Child death rates per million. England and Wales 1931–1960**



Source Registrar General Statistical Review, Part One

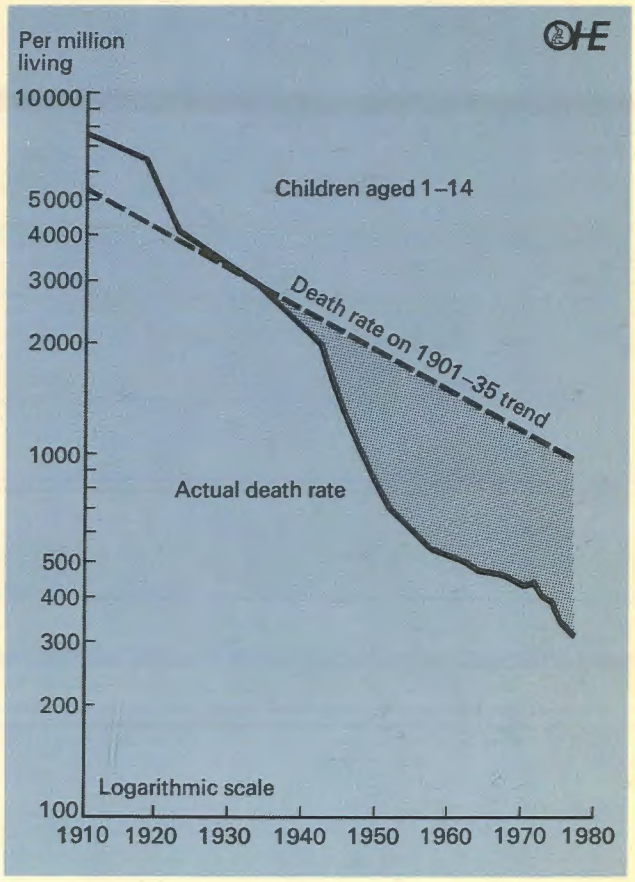
deaths from measles, rheumatic fever and scarlet fever fell steadily, although in these cases the association with the early use of antibiotics was less clearcut. For measles it was not until the introduction of the vaccine in the 1960s that the number of cases fell sharply. With whooping cough, from the 1940s onwards, deaths again fell more rapidly than before. In this case, however, the use of the vaccine which virtually eliminated the disease will be discussed more fully in the next section. Finally, it is worth mentioning the infections of the ear, otitis media, which in many cases prior to the introduction of antibiotics necessitated the classic, painful and dangerous surgery of the mastoid. This operation, and the distressing disfigurement which it sometimes caused, has been made almost obsolete by pharmacological progress.

Figure 3 shows the overall effect of the introduction of vaccination, sulphonamides and antibiotics on the downward trend of childhood mortality. The gap between the actual death rate and that predicted on the 1901–35 trend is shown as the shaded area on the graph. The difference in trends for the years from the 1940s to the 1970s indicates that a quarter of a million people are alive today who would have died during their childhood had there been no improvement in mortality due to modern pharmacology.

Apart from the striking and easily quantifiable examples of tuberculosis and childhood infections there is a whole catalogue of diseases in which therapeutic progress has had a decisive effect. One highly emotive example is 'childbirth fever', because of the special tragedy involved in the death of a mother at the time that her child is born. Childbirth fever, or puerpural sepsis, was the commonest cause of maternal mortality in obstetrics until the introduction of the sulphonamides and antibiotics. Figure 4 shows the number of maternal deaths per 100,000 live-births from the 1940s to the 1970s. The same steep reduction which was seen in earlier graphs is once again evident, dating from the pharmacological breakthroughs of the 1940s and 1950s. The number of deaths from childbirth fever itself fell from 647 in 1935 to 2 in 1977.

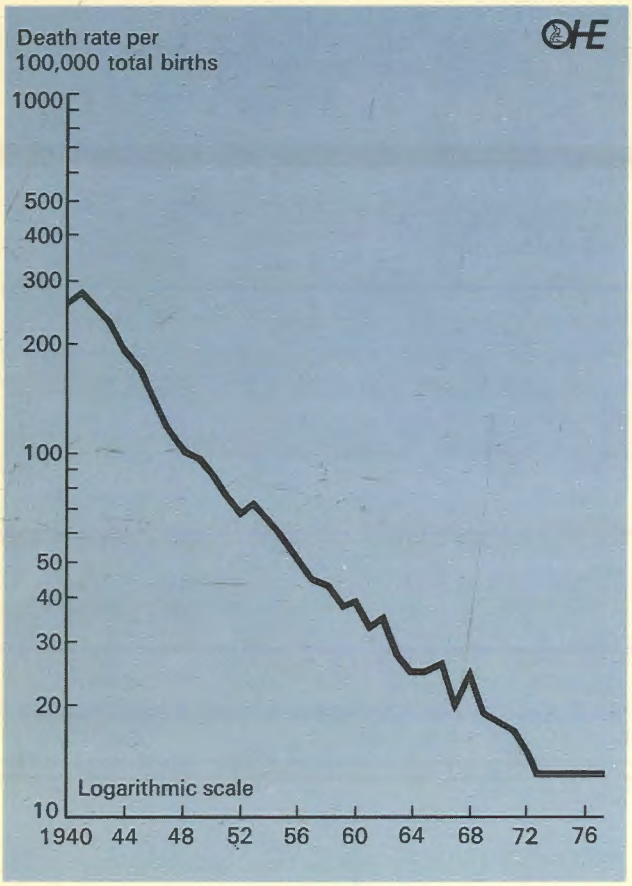
Lobar pneumonia in young adults also deserves special mention. Together with tuberculosis, this was one of the classic causes of premature mortality until the 1930s. There was no specific treatment and all that could be done was to nurse the patient until the 'crisis' of the disease occurred. Even at this stage there was nothing but sympathy and prayer which could be offered to help the

3 Child death rate per million living. England and Wales 1911/15–1977. Five yearly averages 1911/15–1961/65. Annual rates 1966/77.



Source Registrar General

4 Maternal deaths: rates per 100,000 total births, 1940–1977. England and Wales



Source Registrar General's mortality statistics

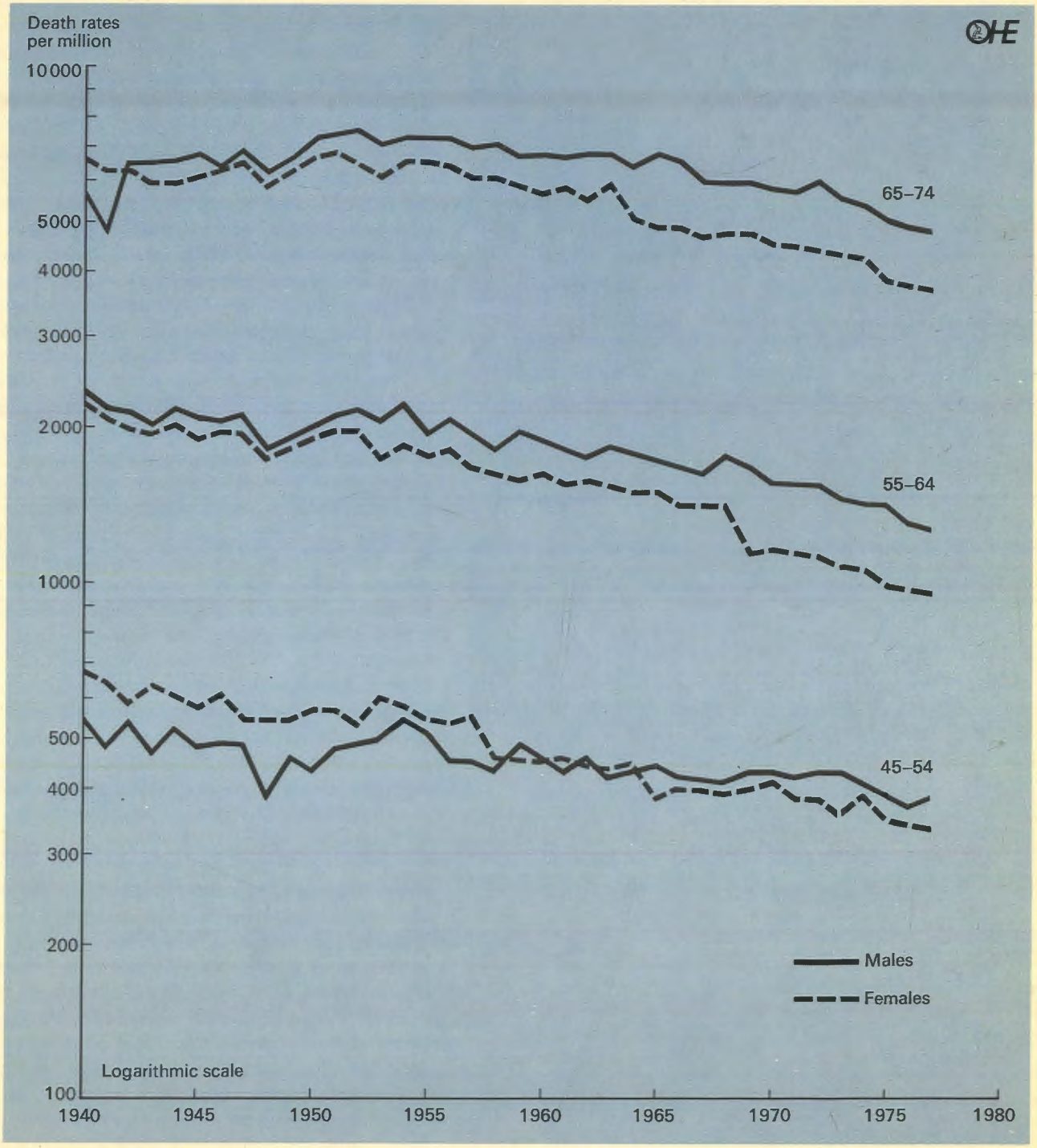
patient to survive. The crisis of lobar pneumonia epitomised the paucity of effective therapy in the early part of this century. Then in the mid-1930s Lederle Laboratories in the United States invested huge sums of money in the development of a series of vaccines for the treatment of pneumococcal infections and so provided the first effective way of dealing with the infection. The financial risk in pharmaceutical innovation, however, was dramatically illustrated when this whole investment was rendered obsolete by the development first of the sulphonamides in the late 1930s and then of the antibiotics in the 1940s. These provided a much more effective treatment and totally changed the pattern of mortality from lobar pneumonia. For young men aged 25 to 34 years the mortality rate dropped by over 95 per cent between the early 1930s and the late 1950s.

Turning away from the contribution of the antibacterial substances to other lifesaving developments, cardiovascular disese is another area in which there has been significant therapeutic progress. Here there have been three main types of advance. The first is in the development of the diuretics. These are important in achieving rapid excretion of excess body fluid in heart disease: this is the treatment of classical 'dropsy'. They are also important, however, in the control of mild hypertension, in this case reducing blood pressure by their action of helping the body to excrete excess fluids. The second group of medicines for the control of blood pressure are the more specific antihypertensives, of which methyldopa is one of the most commonly used. These transform the lives of those previously severe cases incapacitated by high blood pressure, and have with other developments gradually reduced the number of deaths due to cerebrovascular disease (Figure 5).

Thirdly, there has been the more recent introduction of the so-called 'beta-blockers'. These block certain nerve impulses to the heart. They control the heart rhythm and reduce the heart's demand for oxygen. Hence they are a specific treatment for heart disease. In addition, they have a further lifesaving role in the treatment of hypertension and may have other valuable uses such as the treatment of the physical symptoms of anxiety.

Another highly emotive area in which there has been notable progress in the reduction of mortality in more recent years has been in childhood leukaemia. It was only because so many other causes of childhood death had been eliminated or reduced to negligible proportions that by the 1960s the cancers (along with accidents) assumed such a

5 **Cerebrovascular disease. Death rates per million living by age and sex. England and Wales 1940–1977**



Source Registrar General's mortality statistics

leading role among the causes of child mortality. With childhood leukaemia, there was little or nothing that could be done for victims almost until the last two decades. Now with advances in cancer chemotherapy many of the children who develop the disease can hope to survive to live normal adult lives, and results are improving with every year that passes.

Turning from mortality to morbidity, and returning to the contribution of the antibiotics, venereal diseases are an important area where the disease can usually be cured and serious symptoms prevented. Although there is a continuous risk of penicillin and antibiotic resistance developing in the causative bacteria, treatment has nevertheless in practice continued to be effective in the venereal disease clinics over the past 25 years. This is a particular field where the risks of the historical treatments with the toxic arsenical compounds have been eliminated, and where modern therapy has prevented the serious ill effects of the disease such as congenital syphilis, 'general paralysis of the insane' (GPI) and blindness at birth due to maternal gonorrhoea.

Next there are a number of serious diseases which have been controlled by other specific advances in chemotherapy. A notable example here is Wilson's Disease. This is a very rare condition, for which a pharmaceutical manufacturer specifically synthesised and manufactured the compound penicillamine as a routine treatment. This chelates the excess copper which the body is otherwise unable to excrete in this disease. Again more recently, it has been found that another chelating agent has proved even more effective than penicillamine in removing the copper. It is significant, however, that in this case the safety regulations concerning the introduction of new commercial medicines have become so restrictive and expensive to the manufacturer that no industrial firm has been able economically to take up the production of the new compound. The significance of this sort of example will be further discussed in the final section of this paper.

Another very recent development of a specific therapy has been in the pharmacological treatment of stomach ulcers. Here the preparation cimetidine selectively inhibits the excessive secretion of stomach acid which causes the ulcers. Its eventual role as a prolonged and perhaps lifelong therapy has still to be established; but it seems likely that it will provide a safe alternative to surgery in the control of otherwise recurrent stomach ulcers which would not previously have responded to antacid tablets and mixtures. Yet another recent advance suggests that it may soon be possible to treat most cases of gallstones pharmacologically, with an oral agent which dissolves them, once again instead of having to resort to potentially hazardous surgery.

Other examples of specific treatments for the control of serious symptoms come in the group of diseases for which 'replacement therapy' has been developed. Here an essential biochemical substance, which for some reason a particular individual is unable to synthesise naturally, can be replaced by oral tablets or injection. One of the earliest and best known examples is diabetes, where the use of injectable insulin not only controlled the symptoms but has been lifesaving. Here the original breakthrough came with the discovery and isolation of insulin from the pancreas by Banting and Best in the 1920s. However, improved, more versatile and purer insulins have been developed in industry over the past 30 years, and they have been supplemented by a range of oral anti-diabetic preparations. These relieve the patient of the necessity of regular self-injection. As a result of these advances, and perhaps more particularly through the control of the complications of diabetes, for example with the antibiotics, the death rates in younger patients have fallen markedly in the past 30 years. In the under 15 age group, for example, the diabetic death rate fell from 10 per million population in the 1930s to 2 per million in the 1970s.

Another specific example of replacement therapy comes with pernicious anaemia. In the 1930s the only treatment was an expensive and unpalatable diet of raw liver, to replace the Vitamin B12 which the body was lacking. In the 1940s, however, this specific vitamin was isolated and then synthesised, originally as cyanocobalamin and later as the more effective compound hydroxycobalamin. The disease is therefore now treatable with injections and mortality from pernicious anaemia has been cut by three-quarters since 1945. This is another typical disease for which the pharmaceutical industry has made available to the medical profession a specific treatment for a previously often intractable condition.

Finally, among the examples of replacement therapy, there is Addison's Disease. Here the introduction of the corticosteroids transformed the prognosis for a previously lethal disorder of the adrenal glands. Before replacement therapy was available it caused anaemia, weakness and low blood pressure; it affected the heart and the skin; and it frequently led to death from supervening infections or other causes.

Next, there are the other diseases for which the relief and control of symptoms has proved an important advance. These were never particularly life-threatening conditions, but their effective treatment has in many cases transformed the lifestyle of their victims. As examples here, arthritis and rheumatism have been the subject of a number of major therapeutic advances, even though the underlying mechanism of the diseases has still to be understood. In particular both aspirin and the steroids, and more recently a new generation of non-steroidal anti-inflammatories, give a marked degree of relief to many sufferers from rheumatoid arthritis. With modern medicines, and the use of better physical treatments, it is now less usual to see the grossly distorted joints and hands which characterised the often uncontrolled disease in the 1930s and 1940s.

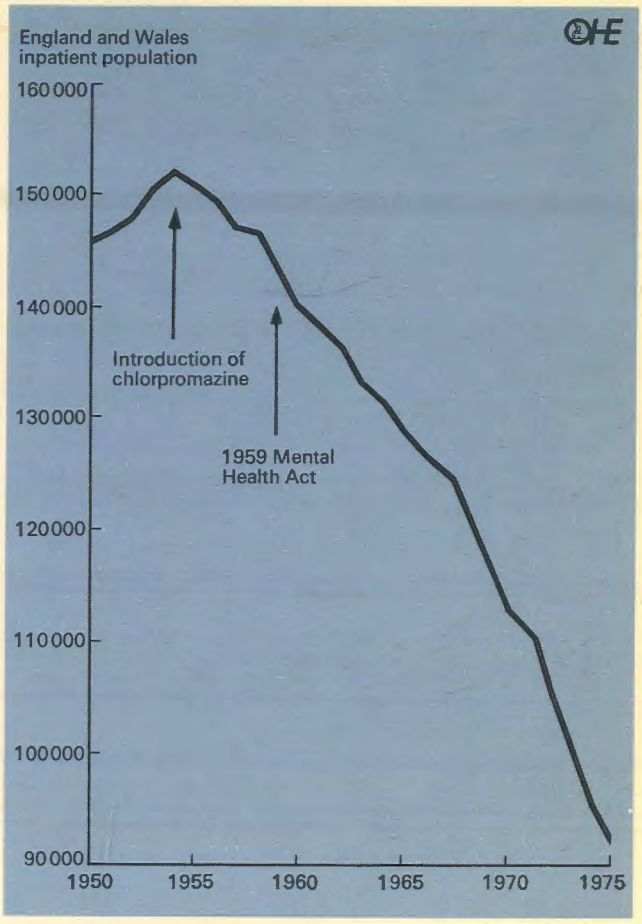
Gout is another rheumatic disease for which there has been a very specific advance. Here the development of allopurinol can often bring complete relief for a previously intractable and painful condition and prevent its common progression into death from renal failure. Less specifically, the modern muscle relaxants, combined with analgesics, have helped to give relief from musculoskeletal conditions of the back, including lumbago and sciatica.

Asthma and hayfever are two allergic conditions which have also benefited greatly in symptomatic terms from pharmacological progress. For hayfever a huge range of alternative antihistamine preparations is available. One or more of these can usually provide relief from the distressing nasal and ocular symptoms which had incapacitated many people either during the pollen season or when they were exposed to other specific allergens. The availability of such a wide choice of preparations is important because many cause side effects such as drowsiness, whose incidence with the use of particular preparations varies greatly from individual to individual.

For asthma, the inhaled preparation disodium cromoglycate has a preventive effect for many sufferers. In addition, symptomatic relief during attacks is available from the use of other inhalers, originally containing isoprenaline, and more recently salbutamol and terbutaline. Desensitising injections and the use of corticosteroids are other methods of helping to gain control over the disease. Asthma will, however, be discussed again more fully in the next section on risks of medication.

Next in terms of symptomatic relief there is the wide range of skin diseases. Here again the family doctor could give very little in the way of effective

6 Mental illness hospitals and units. England and Wales inpatient population 1950–1975



Source DHSS statistical reports

treatment in the 1930s, and the specialist dermatologists were largely restricted to the use of messy and non-specific preparations such as tar ointment. Since then the systemic anti-histamines and the topical corticosteroids have provided a rapid and effective treatment for allergic skin disorders, and the antibiotics have provided relief from bacterial skin infections. In addition, the specific antifungal agents have provided treatment for conditions such as athletes' foot. The most notable change in practice which these new preparations have brought about is to enable the family doctor to cure most skin conditions quickly and without difficulty. It is only the few more intractable cases which now need to be referred to a consultant dermatologist.

Another group of diseases in which there has been major and very significant pharmacological progress has been the mental illnesses. Here both long-term major incapacitating disease and relatively minor anxieties and depressions have yielded to the very wide range of psychiatric medicines which has been developed in the last 20 years. Figure 6 shows the number of patients in mental hospitals from 1953 to 1977. It shows an increasing trend until 1954 when the first psychotropic medicines were introduced, and since then a steady decline. The numbers resident in mental hospitals in Britain fell from over 150,000 in the mid-1950s to less than 90,000 in 1977. Most of these 90,000 were either short-stay patients receiving active, and usually successful, treatment or else they were the psycho-geriatric patients over the age of 65. The reduction in the numbers in hospital has resulted primarily from the effective treatment of those younger patients who could previously have expected to spend a lifetime in a mental hospital, in the absence of any specific therapy for their psychoses.

Of these psychoses, the most effective pharmacological advances have been against severe depression, for which the tricyclic anti-depressants (so called because of their chemical structure) and the monoamineoxidase inhibitors (MAOI's) have proved remarkably successful. There is, as yet, less effective therapy available for schizophrenia, although here there has also been important progress with the long-acting phenothiazines.

Apart from the serious mental illnesses, or psychoses, there have also been great advances against the minor mental illnesses, the neuroses. In particular the benzodiazepines have made life bearable for many who previously suffered almost intolerable anxiety states. The treatment of mild depression is also an important advance: no longer are people expected merely to 'grin and bear it' when life seems intolerably unhappy. It can be conjectured, in this context, that the use of the antidepressants contributed to the marked reduction in suicides which occurred in Britain in the 1960s. Recorded suicide rates fell by one-third between 1963 and 1970.

Finally, in the broad context of mental illness, there is the treatment of insomnia. Here again there has been notable progress, once again most recently with the development of the benzodiazepines, and with other specific and relatively safe hypnotics. Whereas earlier preparations often caused day-time drowsiness or 'hang-over' effects, these can now be avoided. The history of the treatment of insomnia, however, includes the thalidomide tragedy and the earlier widespread use of the barbiturates. These events will be discussed in the next section; here it is necessary only to emphasise that modern treatments for sleeplessness are now very much safer and more effective.

Apart from the diseases referred to above, for which there have been significant advances, it is also worth mentioning some diseases for which there have been no spectacular breakthroughs, but for which there have nevertheless been worthwhile, if less dramatic, progress in the control of symptoms. Bronchitis, epilepsy and migraine are examples. For none of these can modern medicine claim a cure or complete relief. However, the antibiotics undoubtedly reduce the frequency and severity of attacks in chronic bronchitis. The barbiturates and other anti-spasmodics in many cases offer prevention of epileptic attacks; and analgesics and other preparations can help to alleviate migraine.

Next, in this section, two other subjects need to be mentioned. The first is oral contraception. Once again this will be discussed more fully in considering the risks of medication, but it would be wrong to exclude it from any discussion of the benefits. It is difficult to quantify its contribution either to marital happiness or in the specific control of unwanted pregnancy with all its social implications. However, there is no doubt that oral contraception has been a major advance which has brought happiness to many and prevented unhappiness in many others. The contraceptive hormones and related compounds also have other important uses in gynaecology, and many people would not be alive today had it not been for these preparations.

The other much more tangible area for discussion is the contribution of pharmacology to anaesthesia and surgery. Here, the earlier hazards

The risks

of traditional methods have already been mentioned. However, it is also important to emphasise more positively that virtually all complex modern surgery is dependent on safe anaesthetic agents (capable, for example, of maintaining unconsciousness for six to twelve hours, while surgery continues). It also relies on a variety of available 'muscle relaxants'. Before these were developed in the 1940s and 1950s muscles had to be relaxed for the surgeon's knife by the depth of anaesthesia itself. Such deep anaesthesia was not only dangerous but could not be maintained for any length of time. Hence the importance of muscle relaxants. Other specific agents such as the anticoagulants may also be important, for example, in heart-lung surgery. Finally, the antibiotics have made an important contribution to surgery by preventing and controlling post-operative infection.

When one compares the scope of surgery today with that in the 1930s, it is clear how much modern pharmacology has contributed to progress in this field. Brain surgery, heart surgery, joint-replacement operations and heroic repairs after accidental injury have all been made possible by pharmacological progress. The highly skilled surgeons of today could not be attempting their more spectacular operations without modern anaesthetics and other pharmacological agents.

Finally, there should be some specific reference to the whole field of prevention and early diagnosis. This has played an important part in the control of infectious diseases which have already been discussed. However, the principle that 'prevention is better than cure' is so deeply ingrained in public attitudes to health that it is appropriate to end this section on the benefits of therapeutic progress by another reminder of the pharmaceutical industry's contribution in terms of the development of vaccines and immunisation. Although many of the fundamental discoveries, such as smallpox vaccination, were of course made many years ago by the medical profession, it is the industry which has largely developed the actual vaccines in use today. Similarly, many of the diagnostic materials – for example in the early screening for diabetes – are industrial developments.

Healthy living – exercise, sensible diet and avoidance of cigarette smoking – will always remain the backbone of preventive medicine and the promotion of positive health. However, specific preventive measures such as immunisation have also made a major contribution and must continue to do so in the future.

The benefits of modern progress, however, provide only one side of the picture. It has already been pointed out that spectacular progress on this scale was unlikely to have been achieved without some adverse side effects, and these indeed have occurred. This section describes the price which has been paid for progress in terms of these pharmacological misadventures.

Up to the 1930s, death caused by therapy was largely taken for granted and if the patient's condition deteriorated under treatment, the deterioration was usually tactfully ascribed to the disease rather than to the activities of the doctor. Thus the concept of iatrogenic disease[6] is largely the product of therapeutic progress. Since the 1940s a successful outcome of treatment could often be expected, and if instead the patient died or developed serious untoward symptoms the treatment is often (and sometimes unjustifiably) suspect.

Historically an early calamity was the Lübeck disaster with BCG vaccination against tuberculosis in Germany in the mid-1930s. In this, live virulent tubercle baccilli were taken by mouth instead of BCG and as a result 72 out of 251 'vaccinated' infants died of tuberculosis.[7] Another calamitous episode with modern medication occurred in the United States in 1939. An elixir of sulphanilamide was produced using ethylene glycol as a solvent. This compound proved toxic and 107 people died after taking the elixir.[8] As a result of this accident the American Food and Drug Administration introduced the first regulations to control the testing and marketing of new medicines.

Subsequently, during the 1950s, there were further mishaps in France with the preparation Stalinon, and in the United States with the Cutter Laboratories' polio vaccine.[9] Each resulted in tragic deaths and incidentally both were disastrous for the manufacturers concerned. However, it was not until the thalidomide tragedy in the early 1960s that world attention was finally focused on the problem of potential toxicity from modern medicinal compounds.

Thalidomide was an apparently safe mild hypnotic

6 That is, disease generated by the treatment itself.

7 Die Sauglings-tuberkulose in Lübeck Arb. Reichsgesundh. Amt. 69, i (1935).

8 Crout J R. The Nature of Regulatory Choices. Center for Study of Drug Development. (1978).

9 Stalinon was a remedy for boils marketed in France in the late 1950s. Because it contained larger quantities of a compound of tin than those used in its clinical evaluation, it is alleged to have killed 102 people and left at least another 100 permanently affected. (See *British Medical Journal* i; 1958, p 515). For details of the Cutter incident, see page 24.

developed in the late 1950s by a relatively small pharmaceutical firm in Germany. In Britain it was licensed to the Distillers Company Ltd, who at the time were attempting to diversify out of the alcohol market into pharmaceuticals and other biochemicals. In Germany, the tablets were on free sale to the public. In Britain, although their sale was theoretically unrestricted, their use was promoted only for prescription by doctors. At the time of the thalidomide tragedy, the compound had not yet been marketed in the United States, because it was still under review by the government Food and Drug Administration.

In 1962 it was reported from Australia that there appeared to be a connection between mothers who had taken the medicine and those who bore offspring with very characteristic congenital deformities, usually typified by the gross malformation of legs and arms. As soon as these reports were received and confirmed, the medical profession was warned by a letter from the British manufacturers to the *Lancet* and thalidomide was withdrawn from the market. However, as the foetal damage was caused during the first three months of pregnancy, deformed 'thalidomide' births continued to occur throughout 1962. In all, between 400 and 500 babies born in Britain were affected as a result of their mothers having taken thalidomide.[10] Adverse publicity centred on the issue of compensation for the victims and continued for many years. It was a particularly burning issue because thalidomide was taken merely for sleeplessness, and because young children were so dramatically affected.

This tragic episode not only led to Britain setting up a new Committee on the Safety of Drugs, but altered the whole climate of opinion towards therapeutic progress. The many new medicines which had previously been hailed as 'wonder-drugs' became part of a process of innovation which was now seen as possessing potential for evil as well as for good.

The only other widespread adverse reaction which has occurred in Europe since the 1930s was about thirteen years later in the mid-1970s and involved the ICI 'beta-blocker' practolol. The compound was marketed for the treatment of heart disease in 1970. Unexpected adverse reactions were first reported in mid-1974, when characteristic symptoms of damage to the eye were observed. This led the company and government to issue warning letters to prescribers and pharmacists alerting them to the possible risks. Further cases were reported, including damage to the stomach area, the ears and other, rarer effects. As a consequence, as the evidence built up but taking account of the benefits of the medicine and the incidence of the adverse reactions, the use of the medicine was restricted and eventually in 1976 it was withdrawn altogether from the market. By that time other beta-blockers had been developed which had many of the then unique beneficial properties of practolol without the specific adverse reactions; however, practolol is still regarded by some doctors as the treatment of choice in hospitals if the heart rhythm goes out of control.

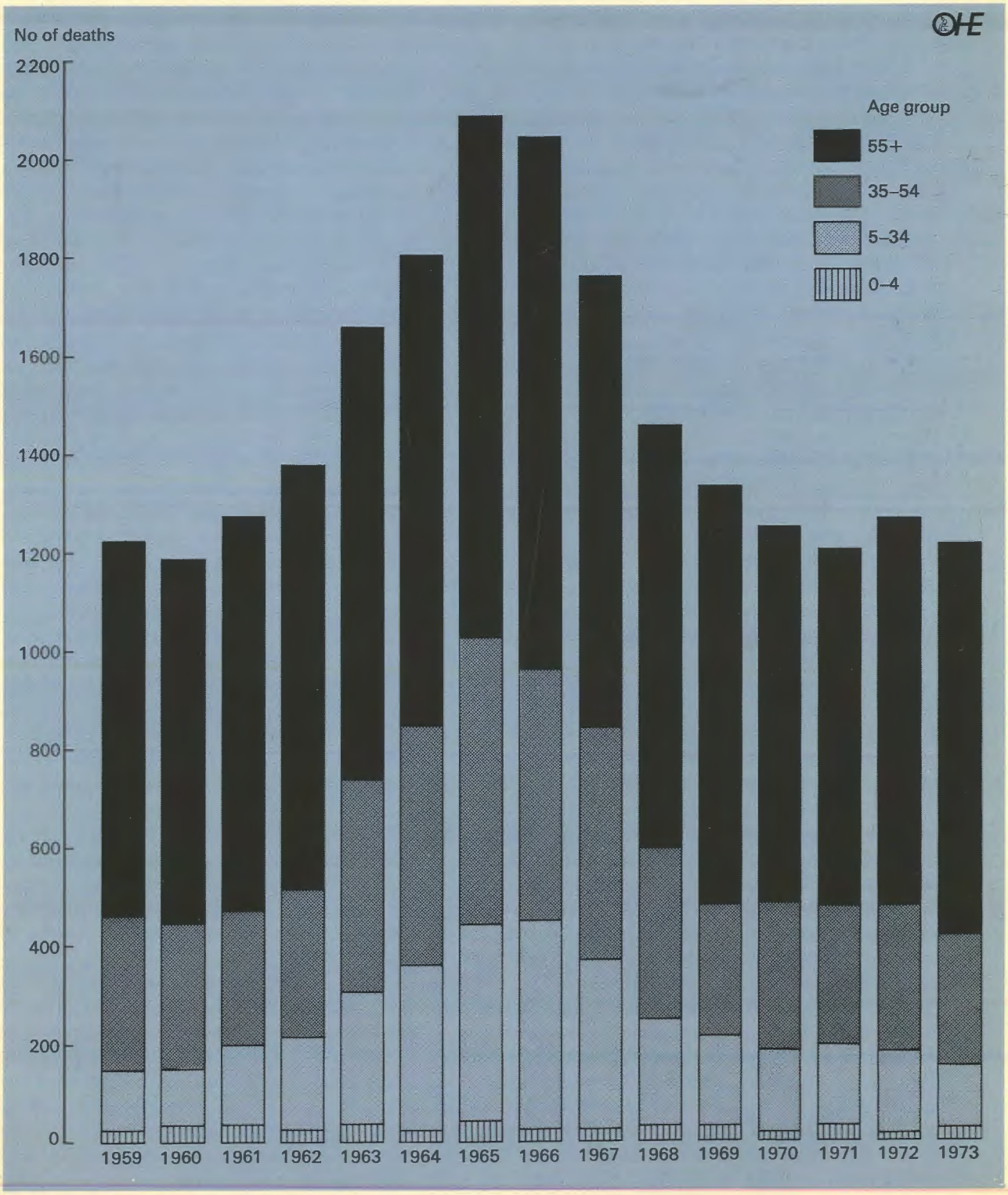
The atmosphere created by thalidomide in the intervening thirteen years had led to a climate in which those who suspected they had suffered an adverse reaction immediately expected compensation, even though in the case of practolol – unlike thalidomide – a lifesaving medicine was involved. ICI took the view that, even though the adverse reactions had been completely unforeseen and accordingly there was no legal liability, there was a case for paying some compensation to patients who had suffered permanent injury because the medical profession was also unaware of the possible appearance of these adverse reactions – in fact, despite exhaustive research, the reason why this one medicine produced these particular reactions has still not been discovered.

Practolol received widespread publicity and this undoubtedly increased the number of claims for compensation and the general level of expectation. But there was a complicating factor as some of the adverse reactions had a similar appearance to naturally occurring symptoms of the ageing process and there were accordingly many cases in which, on close examination, practolol was shown not to have been involved. ICI has received 2,600 claims; payments have been made in 1,200 cases ranging from a few with serious reactions including blindness to many with relatively minor injuries; 1,000 have been rejected and the remainder are still being evaluated.

Nothing can minimise the tragic significance particularly of the thalidomide case. However, it needs to be emphasised that thalidomide and practolol are two isolated episodes in the last 30 years to be seen against the overall background of dramatic therapeutic progress which has already been outlined. The contrast between the benefits and risks which this statement implies will be discussed more fully later.

10 The exact number of 'thalidomide babies' will never be known because in at least 100 cases it is uncertain whether or not the deformities were due to thalidomide. The Distillers Company has so far paid out over £20 million in compensation to about 400 cases where the connection was reasonably certain.

7 Mortality from asthma, by age group. England and Wales 1959–1973



Source Registrar General, Medical Tables, various years

Apart from these two cases, there have also been others where medicines have been withdrawn from use because they were considered too toxic to justify their continued availability. However, in none of these other examples had widespread harm been done before the risks were recognised. Indeed in many cases the risks had been recognised when the medicines were still undergoing clinical trials and had not yet been put on the market. Even with other medicines which had been marketed and which were then discovered to have toxic effects, they were discovered at a much earlier stage than with thalidomide or practolol and the danger from adverse reactions was largely pre-empted. The measures now taken to help to make further tragedies even less likely will be discussed later.

In addition, there have been other much publicised episodes where risks have been discovered or suspected, but in these cases any possibility of such risks have subsequently been minimised by altering the recommendations for use of the medicine without withdrawing it. One of the most recent examples in this category is with the use of oral hormones as a method of testing for pregnancy. Here it was alleged that if the test was used when the woman was pregnant, the test compound itself might be liable to damage the young foetus. This has led to a discontinuation of the use of these hormones for the purpose of pregnancy testing, and to instructions that they should not be taken at all if pregnancy is suspected. In other situations these hormone preparations are apparently harmless.

A perhaps more interesting example is with the treatment of asthma with the pressurised aerosols containing isoprenaline, orciprenaline, isoetharine and adrenaline.[11] Here it was noticed that there was a marked rise in asthma fatalities between 1961 and 1967, mainly in children (Figure 7). It was deduced that this was associated with a corresponding rise in the use of pressurised asthma aerosols, and that the most likely explanation was excessive use of these aerosols and an undue reliance on them at times when more specific measures for the treatment of an asthma crisis were called for. Once the risk had been recognised, and proper publicity given to it by both the manufacturers and government in 1967, Figure 7 shows that the mortality fell again to its former level. In this case inadvertent misuse of what should have been an inherently safe medication appears to have been responsible for an epidemic of fatalities.

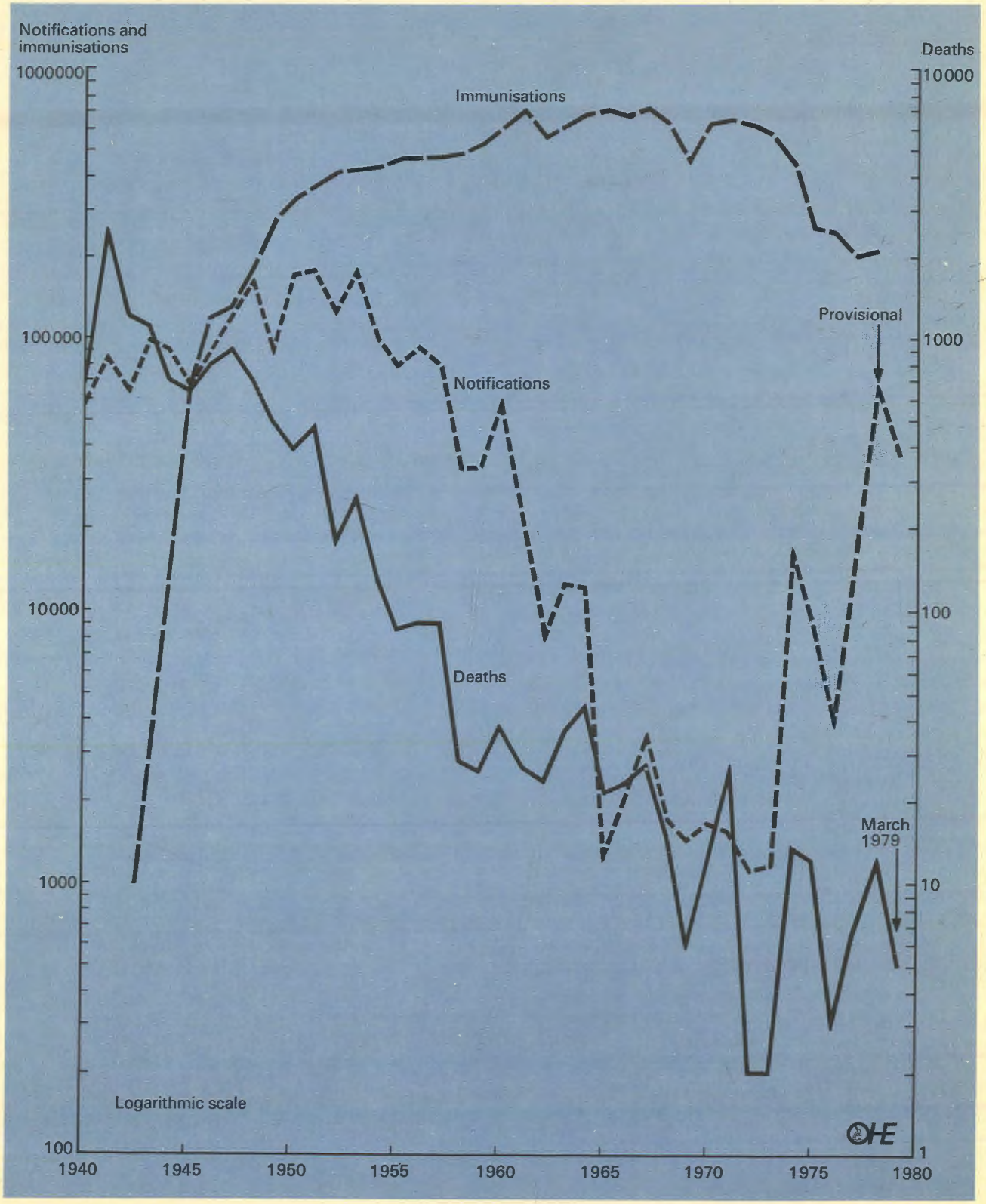
Two other examples are chloramphenicol and streptomycin. Each is a very effective antibiotic of unquestionable medical value. However, in the first case, chloramphenicol was found to be a cause of a serious and irreversible blood disorder. In between 1 in 20,000 and 1 in 100,000 cases, this led to death from infections which were no longer controlled by the body's immune mechanism. In the second case, streptomycin was found to cause deafness through nerve damage. In each of these cases, when the dangers were recognised, the medicines were used with greater caution and wherever possible safer antibiotics were used in their place. In general, an awareness of their risk has helped to minimise its impact, although they remain the antibiotics of first choice in specific diseases and for particular patients.

The last example in this category of medicines, where better understanding can reduce the risk, is with the monoamineoxidase inhibitors (MAOI) in the treatment of depression. Here it was noticed that they sometimes led to severe cardiovascular crises. However, it was soon further noticed that these crises tended to occur only when cheese, meat extract or chianti had been taken concurrently with the medication. Now, simple dietary advice to patients on MAOI has reduced the risk of their causing harm.

The next type of case in which adverse reactions have been publicised are those where there is indeed a risk, but it is arguably well justified on balance by the benefit from the particular medication. The prime current example here is whooping cough vaccine. There has been a widespread outcry, stimulated by political zeal, against the dangers of whooping cough vaccine as a cause of possible brain damage. There is no doubt that there is a risk, although its exact incidence is uncertain and depends on such factors as the age at which vaccination is carried out. However, the effect of the outcry has been to reduce the uptake of the vaccine from 79 per cent of children in 1973 to 39 per cent in 1977. The fall in immunisation and the corresponding effect on notifications for whooping cough are shown in Figure 8. Although the incidence of brain damage both from the disease and from the immunisation are hotly debated questions it is likely that on balance the risk of damage is greater from the disease itself in a non-immune population than it is in a population which has been exposed to the 'risk' of vaccination. This was certainly the view of the Government's Joint Committee on Vaccination and Immunisation in a report in 1977. This concluded that, in view of the 'serious hazards' of whooping cough,

11 The case history has been fully written up and discussed in the OHE publication 'Asthma'. (1976).

8 Whooping cough notifications, immunisations and deaths. England and Wales 1940–1979



Source Annual Reports of the Chief Medical Officer MOH/DHSS

vaccination was 'still a measure to be recommended' even though knowledge was incomplete on the incidence of vaccine damage.[12]

This question of an 'acceptable' risk is perhaps seen most clearly at present in the case of cancer chemotherapy. The medicines used are intended to kill human cells – albeit diseased cancer cells. It is, therefore, not surprising that they also have a toxic effect on healthy human cells, and it is generally accepted that the adverse effects of cancer chemotherapy are extremely unpleasant and hazardous. However, these effects are tolerated by the patients in the hope that the chemotherapy may help to arrest the progress of the disease. Furthermore, even the risk that death may be accelerated by treatment rather than the reverse is accepted, because on balance the enhanced chance of survival is seen to justify the smaller proportion of cases in which serious harm is done. This is an echo of the more general attitude from days gone by, when so little medication was fully effective.

Another category of medicine where the adverse reactions have been highly publicised are the oral contraceptives. Table A shows a calculation carried out ten years ago suggesting that the risk of death in using the oral contraceptive was about the same as the risk of the best alternative method (the IUD), when the risk of death from pregnancy through contraceptive failure was combined with the risk of death from the method of contraception itself. For all other methods of contraception, and of course for the unprotected probability of pregnancy itself, the risk of death appeared to be greater than that from taking 'the pill'. Since that table was constructed several new factors have emerged. First as a result of further medical progress the risk of maternal mortality in childbirth has now fallen to about half the 1967 level of 0.26 per 1,000 births used in the table. Second, the risk of mortality from the use of oral contraceptives is now estimated to be considerably higher than in the table.[13] Both of these factors go against oral contraception. However, the overall risk in users of oral contraception is heavily weighted by age and smoking habits. The excess death rate due to the oral contraceptive is estimated at 5 per 100,000 in the 15–34 age group, rising to about 150 per 100,000 at age 45–49. There is also a three-fold difference in the excess risk for smokers and non-smokers. Furthermore against apparently higher risks than those shown in Table A it is hoped that by reformulation of the pill with a reduction in both oestrogen and progestogen content it will be found to be significantly safer. The progestogen-only pill, while not having quite the same level of efficacy as combined oral contraceptives, nevertheless does not appear to carry the same degree of risk of cardio-vascular complications. Thus in this case safety has been increased by intervening pharmacological progress. On balance the present situation seems to be that the oral contraceptives represent an acceptable risk for younger women; but women over the age of 35, and especially those who smoke, would be advised to use an alternative method of contraception. This is particularly the case for an essentially 'social' medication. The position would be different if the risks involved in a lifesaving medicament were being considered.

The categories of risk set out above cover the seriously damaging adverse reactions which have been experienced with modern medicines and which need to be set against their benefits. They of course exclude many other adverse effects, which are important but nevertheless reversible when medication is discontinued. These merely serve to underline the still more or less 'experimental' state of therapy in many fields of medicine. As has been pointed out, the examples also exclude those cases where risks have been identified early and the offending medicine quickly withdrawn from use. However, whilst in no way attempting to minimise the seriousness of all these risks of medication, it is nevertheless interesting to see this relatively short list of calamitous adverse reactions set out alongside the catalogue of benefits which have been achieved.

Before leaving the subject of risks, two other groups of compounds should be mentioned again. The first are the amphetamines. Their use in the 1940s was generally and uncritically accepted even for consumption without prescription. Then in the 1950s their potential hazards, particularly misuse and addiction, started to be more widely recognised and publicised and their use was confined to prescription only. At the third stage in the late 1960s and 1970s, they were not withdrawn or banned, but merely became obsolescent as more effective pharmacological compounds to deal with depression and with appetite suppression became available. Their risks, therefore, were in practice first reduced as a result of technological progress and effective competitive pharmaceutical industry persuasion on doctors. It was only later that their distribution was controlled under the Misuse of Drugs Act.

The second group of compounds is the

12 DHSS Whooping Cough Vaccination: review of the evidence on whooping cough by the Joint Committee on Vaccination and Immunisation. HMSO, London (1977).

13 Mortality among contraceptive users. *Lancet* 8041, 727, (1977).

A **Estimated maternal mortality rates per year among 1 million women using alternative methods of birth control; position as it appeared in 1969**

Birth control method	*Failure rate per 100 women years of use*	*Expected pregnancies per year among 1 million users*	*Women of all ages, annual deaths due to: Pregnancy (assuming maternal mortality of 0·26 per 1,000 births)*	*Method*	*Total*
Oral Contraceptive	1	10,000	3	20	23
IUD	5	50,000	13	Not known	Not known
Condom	10	100,000	26	—	26
Coitus Interruptus	17	170,000	44	—	44
Diaphragm	20	200,000	52	—	52
Safe period	23	230,000	60	—	60

Source Derived from Peel and Potts (1969), Contraceptive Practice; Cambridge University Press.

Notes

1 For ease of illustration failure rates are based on the mean of the highest and lowest estimates shown in Figure 3.
2 The maternal mortality rate in England and Wales fell from 0·26 per 1,000 births (the figure used in this compilation) to 0·19 per 1,000 births in 1970.
3 Following the withdrawal of many brands of oral contraceptives containing oestrogen, the risk of mortality among oral contraceptive users must be assumed to be less than when this table was first published.

Minimising the risks

barbiturates. Again from the 1930s onwards they were regarded as invaluable sedatives and hypnotics and were very widely prescribed. However, once again their disadvantages started to be underlined, particularly by the availability of safer and less toxic alternatives. As with the amphetamines, they have gradually become obsolescent as the manufacturers of safer alternatives have persuaded doctors to change their prescribing habits. In this case there was also a government-sponsored campaign, 'CURB', to discourage their use. However, this played only a small part and was soon abandoned.

These two cases are examples where commercial and industrial innovation and free competition have themselves contributed positively to the benefit/risk balance without bureaucratic interference. Nevertheless, as the next section will describe, it was inevitable that the public outcry caused by the various adverse reactions which have been described should have resulted in the government stepping in to be seen to 'protect' the public interest.

In the first instance, the responsibility for ensuring the maximum safety of medicines must always rest with the manufacturers. As experience of past tragedies has proved, these manufacturers not only have a responsibility to the public but also a direct commercial and economic interest in ensuring that the medicines which they sell are acceptably safe for the uses for which they are recommended. Indeed, they are likely to have an even greater interest in ensuring the safety of medicines in the future. However, this future development will in no way play down the importance of the responsibility which they have always had in this respect. Just as motor car or aeroplane manufacturers suffer commercially if their vehicles prove unsafe, so do the manufacturers of modern medicines.[14]

It is, however, worth remembering that the manufacturer's interest and responsibility for safety was of considerably less significance in the past. When pharmaceutical preparations consisted largely of dangerous compounds such as chloroform digitalis and opium there was no presumption that they would be even reasonably safe in use. The risks historically associated with 'materia medica' (as it was called) were seen more in perspective against the obvious risks of disease itself and the risks of alternative treatment such as surgery, or bleeding with leeches. In those days the responsibility of the 'wholesale chemists and druggists' was largely confined to ensuring the reasonable purity of the medicaments they sold. It was the medical profession, if anybody, who took the responsibility for their safe administration. The deaths due to amethocaine, which have already been mentioned, were still taken for granted even in the 1940s and early 1950s. No one thought to sue the manufacturer when an otherwise healthy child died suddenly as a result of an anaesthetic for a minor operation.

However, since the episode with the sulphanilamide elixir in the United States in 1939 it started to be recognised that it was primarily the duty of the company which developed a new medicine to ensure its safety. This was certainly accepted by the chief chemist, in that particular case, who committed suicide because of his mistake. Nevertheless, it was also accepted in the United States as a result of the sulphanilamide incident that the government must take an interest in order to provide some further assurance that new

14 The DC 10 disasters provide an interesting parallel to the problems faced by pharmaceutical manufacturers in respect of safety.

medicines were safe for the uses for which they were advocated. This was the philosophy behind the original US Food and Drug Administration Regulations which followed the accident with the elixir.

However, still in the United States, the 'Cutter disaster' with polio vaccine in 1955 confirmed that it was still primarily the manufacturer, rather than government, which had the main interest in ensuring the safety of its own medicinal products. In this case a government body, the Laboratory of Biologics Control, had passed the vaccine as safe.[15] Despite this, the vaccine caused 59 cases of paralytic polio and 5 deaths. There was no evidence that Cutter had been negligent, since they had followed the government's manufacturing instructions and since the material had been passed according to the government regulations. Nevertheless, the company was found liable for damages under the laws of warranty. By 1961 they had settled claims of over three million dollars – one million more than the firm's insurance cover.

In Britain it was not until the thalidomide tragedy in 1962 that government decided to get involved in the question of the safety of new medicines. Following that, in 1963, the government set up the Committee on Safety of Drugs which came into operation at the beginning of 1964. This was a voluntary rather than a statutory body, under the Chairmanship of Sir Derrick Dunlop, Professor of Therapeutics at the University of Edinburgh. Once the Committee was established, pharmaceutical companies agreed voluntarily to submit data on new medicines both before they were put into clinical trial in man and again before they were marketed. Companies agreed not to market new medicines without or against the advice of the Committee.

The Committee also set up a sub-committee to watch out for the development of adverse reactions after the new medicines had been marketed. All the arrangements worked well, and were compared favourably with those of the US Food and Drug Administration's by then well-established and extensive bureaucracy.[16] However, in the context of the remarks above, and in the light of subsequent experience, it is significant that the Annual Report of the Association of the British Pharmaceutical Industry for 1963–64 recorded that the existence of the Committee on Safety of Drugs did not 'detract in any way from the ultimate responsibility of the manufacturer for the safety of his products'.

At the same time Enoch Powell, the then Minister of Health, in commenting on the arrangements pointed out that: 'It would be a cruel deception, to which no man of science or professional integrity would lend himself, to pretend that this or any other mechanism can guarantee absolute safety or indeed that, in this field, such a thing as absolute safety exists at all. Our knowledge is imperfect, and as long as pharmaceutical science advances, it will necessarily continue to be imperfect though constantly widening'.[17]

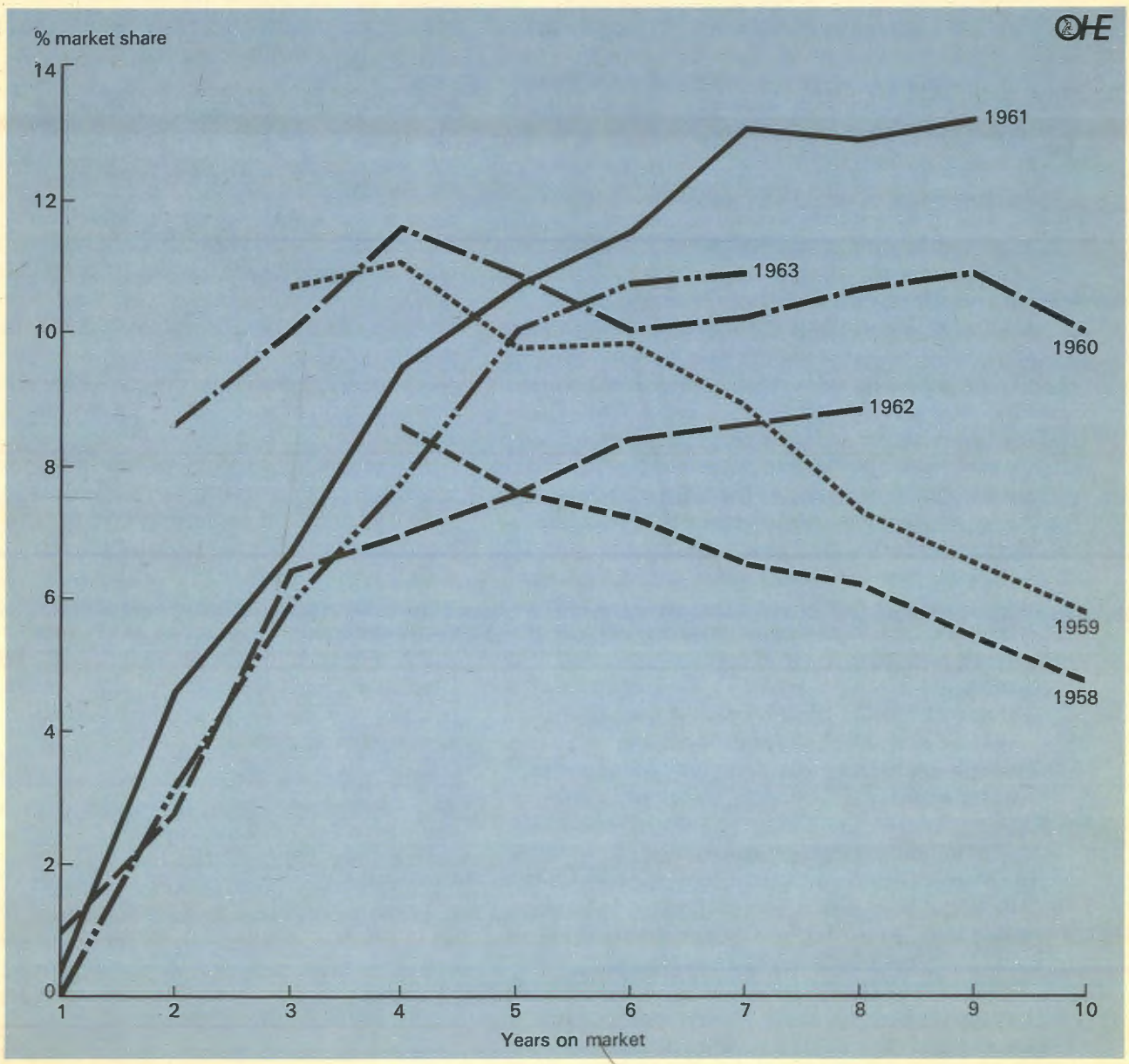
The original voluntary arrangements for the Safety of Medicines in Britain were terminated by the Medicines Act of 1968. This set up a Statutory Medicines Commission (also under the Chairmanship of Sir Derrick Dunlop). Under the Medicines Commission, a Committee on Safety of Medicines was established under the Chairmanship of Professor Sir Eric Scowen to replace the Committee on Safety of Drugs. The new arrangements, which came into operation in September 1971, are still in force. They lay down that the Committee on Safety of Medicines can be called upon to advise the Department of Health as to whether or not to permit clinical trials and whether to grant a licence to enable a new medicine to be marketed. The Commission can hear appeals by the manufacturers if they disagree with an adverse decision by the Committee on Safety of Medicines. The ultimate authority for the grant of 'clinical trial certificates' and product licences, however, lies with the Department of Health.

In practice the Committee and the Commission rely heavily on the advice of the Civil Servants who staff them. The manufacturers in turn are largely in the hands of these Civil Servants as to the speed with which applications to conduct clinical trials or to market a new medicine are handled. The effect of this will be discussed when consideration is given to the proper balance of benefits and risks.

It must be clear from the discussion so far that the establishment of these government procedures for the scrutiny and licensing of new medicines could not ensure their absolute safety, any more than the manufacturers themselves had been able to avoid all risks. Nevertheless, the broad over-view of the Committee on Safety of Medicines and the Medicines Commission could undoubtedly in some cases give a perspective on potential dangers which might not have been available to the individual manufacturers. Obviously, also, the licensing

15 Wilson J R. Margin of Safety, p 106 (1963).
16 Cooper J D. Lean, Spare Apparatus Controls Safety in UK; Int. Med. Tribune of Great Britain. 6 September (1966.)
17 Powell J E. Address to the Centenary British Pharmaceutical Conference, London. *Pharmaceutical Journal*, p 228 (1963).

9 Market share histories of the product introductions of given years



Source Innovative Activity in the Pharmaceutical industry: Figure 1: NEDO: 1973

procedure provides a safeguard against an unscrupulous operator who might be tempted rashly to cut corners in safety testing procedures. It should be emphasised again, however, that past accidents appear to have occurred due to genuine errors of judgement, or more often due to genuine lack of fundamental scientific knowledge on which to base good judgement, rather than any element of recklessness. Such errors will continue to occur because of the imperfect science involved in trying to predict human adverse reactions from available laboratory tests.

Since government committees cannot ensure absolutely safe medicines, considerable emphasis is also placed on government's role in monitoring for adverse reactions amongst those medicines which they have already approved for marketing. There are two elements to this process. First, prescribing doctors are encouraged to complete and to send in 'yellow cards' to report to the Committee on Safety of Medicines suspected adverse reactions. These reports are then processed by computer. If a specific adverse reaction is suspected as a result of these reports, a warning letter is sent to all doctors telling them of these suspicions. This was one of the procedures followed, for example, in the case of the deaths due to aerosol sprays in the treatment of asthma, and when the adverse reactions to practolol were originally suspected. The government letters of warning may be preceded, supplemented or followed by warnings issued directly by the manufacturers, both in letters and through their medical representatives. In practice in the eight years up to June 1979 only 17 warning letters had been issued by government. The one which they issued that month came after a gap of 18 months since its immediate predecessor.

The reporting of adverse reactions, however, is an incomplete process. Many doctors are reluctant to use the government yellow cards because they feel their suspicions may be unfounded, or because they may be uncertain which of several medicines have been responsible for a specific reaction in a patient. Thus secondly, in practice, there is evidence that reports and remarks made to the manufacturers' own representatives may be a better way of learning of suspected adverse reactions. In a survey in 1975, 37 per cent of general practitioners seeing representatives stated that they had reported to the representative an adverse reaction on a medicine they had used in the past 6 months. By contrast only 18 per cent said they had used a government yellow card.[18] These figures once again highlight the predominant role of the manufacturer in helping to assure the safety of medicines. In addition, only the manufacturer, rather than any single national government, can have access to worldwide reports on the experiences with his own medicines in practical international use.

One other factor needs to be mentioned in this discussion of developments to minimise the risks of medicines. This is the apparent strengthening of the natural conservatism of doctors towards new therapies as a result of the thalidomide tragedy. Figure 9 shows the share of the prescription medicine market held by successive cohorts of new medicines according to their age since introduction. Each line in the diagram represents the 'market development' for the most widely prescribed medicines introduced in the year indicated. For those introduced in the years up to 1960, they reached their highest rate of prescribing by the fourth year, and subsequently declined more or less slowly. By contrast those introduced in 1961, 1962 and 1963 did not reach their peak in terms of numbers of prescriptions until the seventh or eighth year. The most likely explanation for this slower uptake of new medicines seems to be that the thalidomide tragedy had made prescribers much more cautious in starting to use recently introduced innovations. They have become more inclined to wait for others to gain experience of the new medicines first.

18 *ABPI News*, No 159, January (1976).

Current developments

There are three current developments of importance in relation to the whole question of the safety of medicines. These are 'monitored release', 'post-marketing surveillance' and the recent Report of the Pearson Commission on Civil Liability and Compensation for Personal Injury.

Monitored release is a technique by which a new medicine is first released on a limited basis, and its use is specifically monitored in the patients for whom it is supplied. In a way it is a form of extended 'clinical trial'. It is, however, specifically intended to pick up reports of adverse reactions, rather than to confirm further the efficacy of the medicine. In 1977, Sullman described the experience with 15 cases in Britain where new medicines were introduced in this way.[19] In eight of these, the monitoring was carried out as a government condition imposed when the medicine was licensed for sale. In the other seven the manufacturers themselves chose to monitor the use of their new medicine.

It is an essential element of monitored release that a specific and suspected adverse reaction is being watched for. It is not intended to pick up totally unexpected reactions, although it will, of course, tend to do so. In any case, the doctor is asked to fill in forms giving his experience with the medicine in the patients to whom he has administered it. The medicine is generally provided free by the manufacturer, although in more prolonged instances it may be prescribed normally. In a monitored release the medicine is commonly confined to use by hospital consultants, rather than by general practitioners.

The principal limitation of monitored release is the small number of patients involved. Typically this would be 1,000 or less. For example, in one case where the licensing authority originally asked for 10,000 patients to be monitored they subsequently accepted that this was impractical and reduced the demand to cover experience with only 1,000. The cost, including payments to participating doctors, works out at upwards of £100,000 per 1,000 patients. The period of monitoring has varied from three months to two years. In practice, based on the results of these 15 schemes, Sullman concludes that the 'new information obtained on adverse reactions has been minimal' from monitored release. Some manufacturers are still keen on the idea. Others specifically question its value in the light of their own negative experience.[20] Hence the greater current interest in schemes for the broader concept of post-marketing surveillance.

Unlike monitored release, the phrase *post-marketing surveillance* is usually applied to the search for *unexpected* adverse reactions. That is, it is looking for the sort of thalidomide or practolol damage which was totally unsuspected when the medicine was first introduced. By analogy, when the terms are used in this way, monitored release is metaphorically looking for a specific type of needle which may or may not be in a given haystack. Post-marketing surveillance, on the other hand, is looking for a totally unknown type of foreign object in a whole series of haystacks which might or might not contain anything untoward. Not surprisingly, therefore, post-marketing surveillance schemes are more difficult to define, have not so far been tried in practice, and would tend to be more expensive than monitored release. The suggested number of patients to be included in such schemes ranges from several thousands to 100,000. Such numbers are necessary to have any reasonable chance of detecting the rarer types of adverse reactions which may occur, for example, in only one in several thousand patients (eg, fatalities from amethocaine or chloramphenicol). If one assumes that 20 new compounds need to be monitored each year in 100,000 patients, and that they should be followed up for three years, the total cost has been estimated to be £240 million a year.[21] This is rather more than the British Pharmaceutical Industry spends on research and development as a whole. A period of three years is necessary when judged, for example, from the practolol experience. In that case symptoms often did not occur for two to three years after first treatment, and might still occur up to two years after treatment had been discontinued.[22]

One of the most practical schemes of post-marketing surveillance which has been proposed involves the use of the standard 'FP10' prescription form. The prescriptions for specified new medicines could be extracted when the forms were being centrally priced, and a sample of prescribers could be asked to report on the patients to whom they had given the medicine. If an untoward reaction was suspected as a result of this original 'sample' approach, every patient given the medicine could then be contacted through their doctor, and thoroughly examined for the

19 Sullman S F. A Résumé of the Pharmaceutical Industry's Experiences with Monitored Release In: Medico Pharmaceutical Forum Publication, No 7 (1977).

20 Harcus A W *et al. British Medical Journal*, 2, 163 (1979).

21 Godfrey D and Bowler E J. Post-Marketing Surveillance; Commercial Implications. In Medico Pharmaceutical Forum Publication, No 7 (1977).

22 Nicolls J T. The Practolol Syndrome – A Retrospective Analysis. *Ibid.*

suspected reaction.[23] The costs for such a scheme would still depend on the numbers and length of time for which surveillance was carried out, but it would probably be considerably less than the estimate given above. A unit to study methods of post-marketing surveillance is proposed for Southampton University.[24]

Turning to the question of *product liability* The Royal Commission on Civil Liability and Compensation for Personal Injury reported in March 1978, and its recommendations are still being debated. As far as new medicines are concerned, the Commission was probably influenced strongly by the thalidomide tragedy, in which the Distillers Company would only have been liable for compensation in law had they been found negligent. In the event, under the pressures of public opinion, and whilst denying liability, the company made substantial settlements out of Court, as already indicated. The Pearson Commission, therefore, is likely to have taken the view that in principle most cases of harm caused by medicines would come in the 'no-negligence' category, and, therefore, in law those who suffered adverse reactions would have no redress for compensation against the manufacturer.

In consequence, the Commission recommended that the law should be changed and that in future 'strict liability' should be imposed on manufacturers of medicines. This would make them liable for the effects of adverse reactions even if there was no question of their having been negligent in the development, testing or manufacture of the medicine. This may seem fair from the point of view of the victim – such as the thalidomide child – but without suitable safeguards for the manufacturer it could have very serious repercussions on their willingness to develop and market new medicines. The pharmaceutical industry has proposed that if there has to be strict liability there should be some sort of government financial protection to safeguard any company which might in the future be involved in another catastrophe such as thalidomide. Clearly a medium-sized pharmaceutical company would simply be unable to produce the current equivalent of the £20 million which Distillers were able to pay in compensation. Nor would it be possible to obtain unlimited insurance cover for product liability: the sums which might be involved are simply too great.

Already in the United States there are indications that companies will not develop and market necessary products because of the risk of catastrophe damages being incurred. For example, no manufacturer was willing to market the recommended influenza vaccine in the winter of 1978–79. This was presumably because the risk of liability for damages through a less disastrous recurrence of the Cutter type of incident deterred them.[25] It appears that in the United States as well as in Britain there is a need for some economic safeguard against claims for damages when strict liability (or liability under warranty in the absence of negligence) exists. Without such a safeguard the balance of public interest seems to be tipped to an undesirable degree against pharmaceutical innovation.

23 Wilson A B. The Pharmaceutical Industry's View of Post-Marketing Surveillance. *Ibid.*

24 *Scrip*, No 451, 5 January (1980).

25 The law on liability has developed along different lines in the United States and in Britain since about 1850.

Some underlying principles

No one is in any doubt that medicines should be as safe as possible in use. However, there is clearly a balance which has to be struck between making new medicines available at all and accepting some risk that they may do harm as well as good. All new medicines must involve some element of risk. For relatively minor disorders, medicines must come as near to absolute safety as can be achieved. This was one of the reasons why thalidomide – a 'mere' sleeping tablet – caused such a traumatic shock when its terrible side-effects were first revealed. For the treatment of more serious, disabling and potentially fatal illness, on the other hand, it has already been pointed out that a known degree of risk may be acceptable. In such cases, it is also implicit that the public and the professions should be prepared to accept an element of unknown risk. Even with practolol, and its serious adverse reactions, it has always been accepted that it had saved very many lives before it was eventually taken off the market. In fact, it has been pointed out that this withdrawal was perhaps only acceptable at all because other heart medicines were on the market as therapeutic alternatives to practolol when it was withdrawn. Thus in the search for greater safety there is always a danger that patients may be needlessly denied relatively safe and valuable medicines – or medicines with a degree of risk which would be acceptable in their particular therapeutic situation. This danger is most obvious because of one factor. There is at present no hard evidence to show the value of more extensive and more prolonged laboratory testing as a method of reducing eventual risk in human patients. In other words the predictive value of studies carried out in animals is uncertain. The statutory bodies such as the Committee on Safety of Medicines which require these tests do so largely as an act of faith rather than on hard scientific grounds.

With thalidomide, for example, it is only possible to produce the specific deformities in a very small number of species of animal. In this particular case, therefore, it is unlikely that specific tests in pregnant animals would have given the necessary warning: the right species would probably never have been used. Even more strikingly, the practolol adverse reactions have not been reproducible in any species of animal except man. Conversely, penicillin in very small doses is fatal to guinea pigs. If it had been tested in those animals before being given to man, its systemic use in humans might well have been considered too hazardous and unethical.

Hence the first problem in minimising risks with new medicines is the difficulty inherent in trying to predict adverse reactions in man from studies in experimental animals. The present tendency is to ask for more and longer animal tests merely in the hope that they may somehow make medicines safer. It has to be remembered that in addition they do three things. First they will in some cases rule out the human use of medicines which would in fact be safe and valuable. Second, more predictably, they delay the introduction of all new medicines. Thirdly, they add enormously to their cost. Perhaps the mere price to be paid is relatively unimportant. However, the more fundamental economic costs of delay will be discussed shortly.

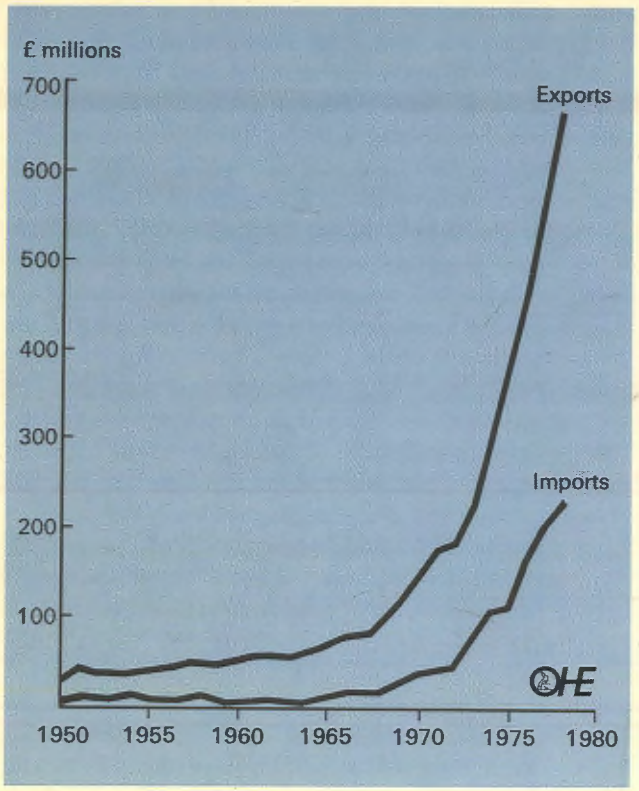
As far as delays are concerned, there are only estimates and impressions of the total effect of current measures to maximise safety. In the 1950s it was generally accepted that it took three or four years at the longest for a newly synthesised medicinal compound to emerge in the pharmaceutical market as a new medicine. Now in the 1980s it is expected to take more than 10 years. New chemicals being synthesised and first tested today may not be available as new medicines until well into the 1990s unless more rational attitudes can be made to prevail.

Returning to the principles, it has been argued that the administrative delays of the Food and Drug Administration in the United States saved the American public from general exposure to thalidomide. It is certainly true that it took so long to process the application that the first evidence of nerve damage (not deformities) had emerged before thalidomide was ready for US approval. Once these reports began to appear, the American authorities became nervous and further delayed approval.

The key point, however, is that the evidence that thalidomide had unexpected adverse effects had only come to light because it was being widely used in clinical practice in other countries. It was not more elaborate laboratory testing which first indicated the potential dangers. Thus, in principle, delay in one country has been shown to be of value only in a case where the medicine was already in use elsewhere. There is no evidence from the United States experience with thalidomide that more prolonged laboratory testing as such would have avoided the human tragedy.

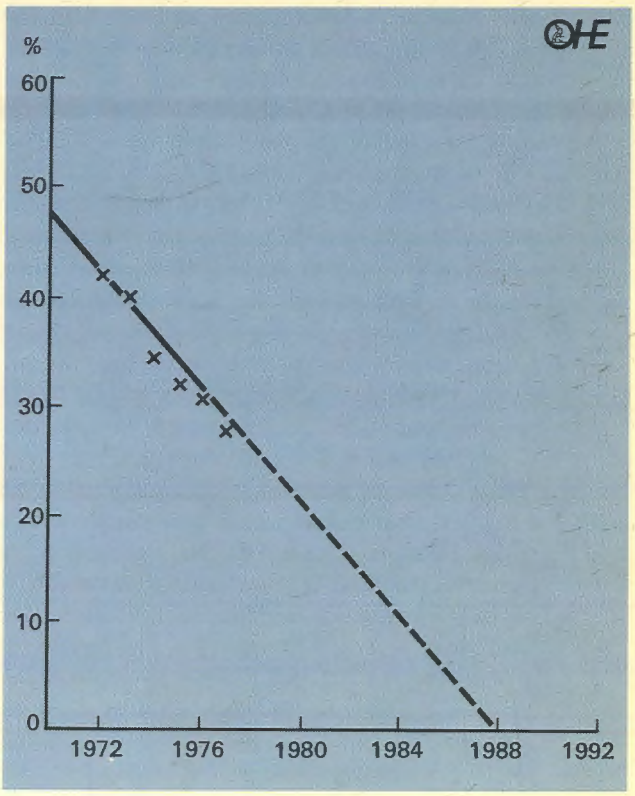
On the other hand the effect of delay can be measured realistically in terms of benefits withheld. For example, it has been claimed that if the introduction of the medicine chlorthiazide (a diuretic for heart disease and high blood pressure)

10 Pharmaceuticals: Exports and Imports 1950–1978



Source Association of the British Pharmaceutical Industry

11 Percentage of Hoechst world-wide R+D budget devoted to innovation: 1972–1977; with arithmetical projection to 1988



Source Cromie B (1979). In: Medicines for the year 2000; OHE

had been delayed in 1957 by the length of time which could have been expected with the system as it prevailed in 1973 it would have taken an extra seven years to become available. During this period it is estimated that 20,000 patients would have died needlessly.[26]

Turning to the economics, there are two aspects to be considered. The first is the parochial British situation. In this country pharmaceutical exports and contribution to balance of trade have grown steadily and steeply since the 1950s. (Figure 10). In 1978, exports totalled £655 million and the favourable balance of trade was £454 million. For the European Community as a whole the pharmaceutical industry in 1977 contributed over $2,000 million to the positive balance of trade. Almost all of this contribution is made up of modern medicines, and hence its continued growth depends largely on maintaining the flow of new innovations. If new medicines are unreasonably delayed in the name of safety, patients as well as the British and European economy will suffer.

Taking the broader picture of worldwide pharmaceutical innovation, a note of alarm has been struck by Cromie of Hoechst Pharmaceuticals.[27] He has pointed out that his company has been able to spend a steadily smaller proportion of its research and development budget on true innovation as a result of the requirements of the international regulatory bodies. As Figure 11 shows the percentage devoted to innovative work has fallen from 42 per cent in 1972 to 28 per cent in 1977. This is a fall of one-third in five years. If the line were to continue downwards on an arithmetical basis Hoechst would have discontinued all innovative work by 1988. This indicates the economic danger for pharmaceutical innovation if current trends in regulatory demands were to continue.

There is a particular problem with medicines for rare diseases. It was pointed out in the case of Wilson's Disease that a new compound has been found to be of special value. This is not available commercially simply because no company can afford to go to the full expense of putting the compound through the licensing procedure when eventual sales would only be for a few hundred patients. The Committee on Safety of Medicines have said that they cannot make an exception and allow 'short cuts' in such a case. In practice, for so few patients the medicine can be prepared in a hospital laboratory without a product licence. However, the general principle of withholding medicines for rare diseases on economic grounds, due to safety requirements, poses a problem which merely accentuates the overall need to strike perhaps a more sensible balance than at present. The point at which it becomes uneconomic to introduce a new medicine will apply to compounds which could benefit larger numbers of patients in the future.

The problem is that no one is able to say where the right balance should be struck. This is largely because of the conceptual difficulty in understanding the risk-benefit equation. In 1977, the Office of Health Economics made an attempt to get prescribing doctors to give some opinion on the acceptable level of risk and on the delay to new medicines which they felt should be suffered to achieve it. The attempt had to be abandoned because the whole problem simply seemed to be unquantifiable to those who took part in preliminary interviews.[28] Doctors would no doubt have found it even more difficult if the problem had been posed in terms of cost rather than delays. It seems that the regulatory bodies themselves and the Civil Servants who staff them face the same dilemma as practising doctors. They simply do not know how much information to ask for, and they are unable to balance the time and cost of gathering the information against the uncertain degree of increased safety to which it might contribute.

On top of the delays in actually carrying out the required tests, there are also the delays within the Committee on Safety of Medicines itself in considering applications put to it. Figures 12 and 13 show the median delays experienced in recent years in the treatment of applications to perform clinical trials and to market new medicines.[29] The former of these delays is probably the most serious and perhaps the less necessary. At the clinical trial stage the new pharmaceutical compound will still be being administered to man under the closest supervision. Hence the risks during clinical trials are in any case minimal. On the other hand a delay in being permitted to start trials in man is highly demoralising for the research workers involved. Just when their hopes

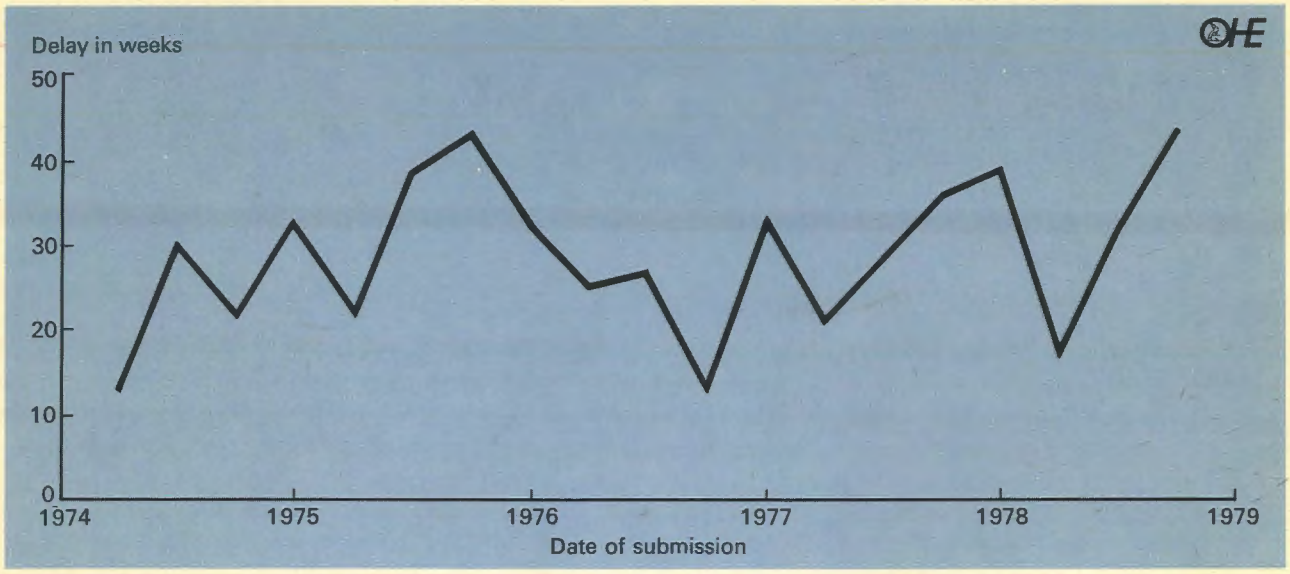
26 Smith T. *Pulse* 39, 1, 27. 7 July (1979).

27 Cromie B W. The Effect of British Regulations in *Medicines for the Year 2000*. Ed Teeling-Smith G and Wells N E J. OHE (1979).

28 Market Investigations Ltd. Private Communication (1978).

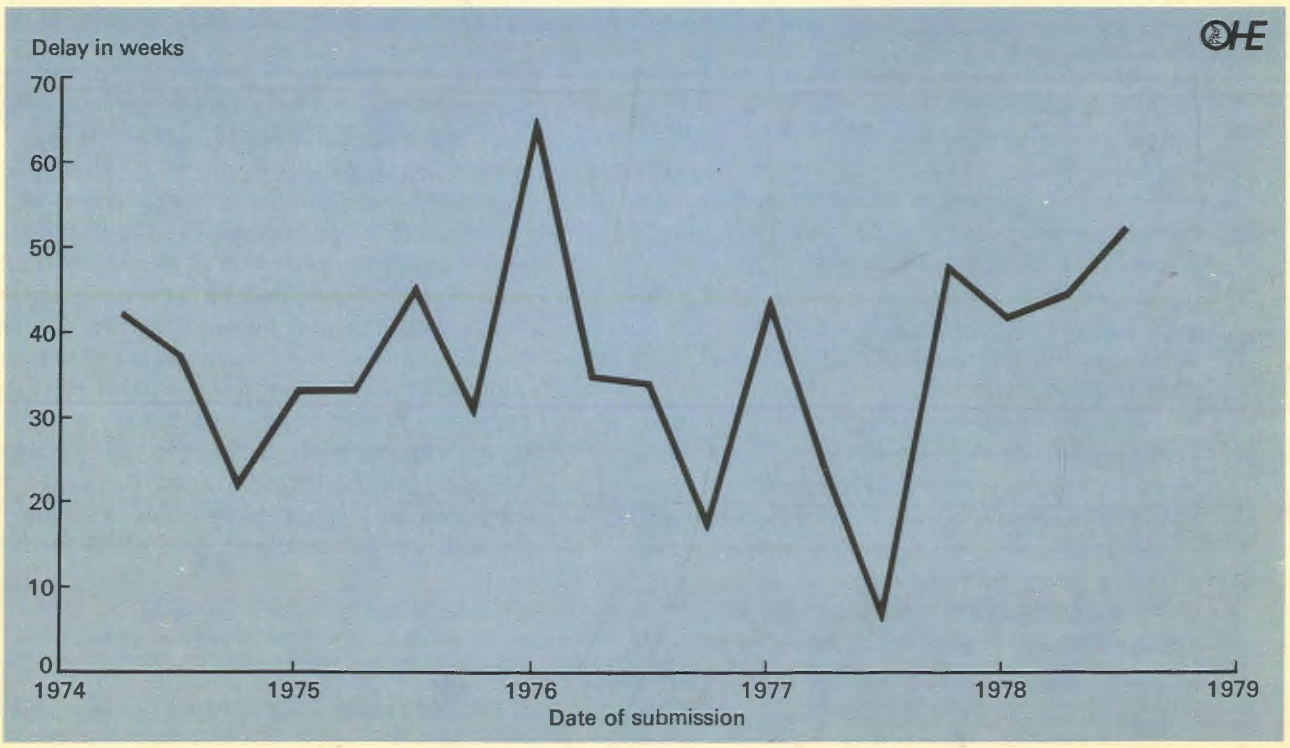
29 Because of the delays, the figures in the diagrams necessarily cease after applications made in 1978. For approvals given between August and December 1979 the average delays had been 6.25 months for a clinical trial certificate and 13.5 months for a new product licence. Both figures are for new chemical entities. For medicines based on existing compounds the figures were 8 months and 7 months respectively. These figures exclude the length of time taken for companies to answer queries.

12 **Median delay between submission of applications for clinical trial certificates for new chemical entities and date of formal decision (or withdrawal)**



Source ABPI Survey

13 **Median delay between submission of application for product licence for new chemical entities and date of formal decision (or withdrawal)**



Source ABPI survey

Discussion

for the compound are highest and when there is most enthusiasm to discover its value in human sickness, everything grinds to a halt while the processes of bureaucracy take their course. In practice, the result has been that most companies have decided to carry out early trials outside Britain, where the same delays are not imposed. This in turn is demoralising for the academic clinical pharmacologists in Britain, who find the most exciting stages of early clinical evaluation denied to them. Fortunately this situation has been recognised by the Secretary of State and a procedure for speeding up clinical trial applications is at present being discussed.

Apart from delays and costs before introduction, there are other cases where medicines have been banned or withdrawn from the market after introduction on what seem to be dubious grounds. These cases concern particularly medicines where very high doses given over the lifetime of an animal have been shown to produce cancers. The American legal position is that any food or medicine which is shown capable of producing cancer in any species of animal must be banned. The British regulatory authorities have tended to follow the same principle with medicines.

One of the most recent examples has been the withdrawal of the antihistamine methapyrilene from the British market on the advice of the Committee on Safety of Medicines. The compound had been shown to be able to produce tumours in rats when administered continuously throughout their lives at 25 to 30 times the dose appropriate to man. It is certainly debateable whether this is a scientifically sound decision as opposed to an emotional reaction to the fear of cancer. It is admitted that there is no evidence that any similar effect would occur in man, and the withdrawal is described as 'a precautionary arrangement.'[30] In this particular case the inconvenience to patients is probably not too great, but the principle of the withdrawal has adverse economic repercussions for pharmaceutical innovation as a whole.

There can be no doubt that pharmacological progress over the past 30 years has made a major contribution to health care. Not only have medicines some notable achievements to their immediate credit, such as the conquest of tuberculosis, but they have also contributed to progress in fields such as surgery and the care of the chronic sick. Although general welfare, such as nutrition and housing, has also made a major contribution to improving health, it is arguable that medicines have been responsible for the most specific and the most economical gains against disease since the Second World War.

Nevertheless, these achievements have been associated with some risks, and with one notable human catastrophe – thalidomide. The consequent balance which has to be struck between benefits and risks is by no means unfamiliar in technological progress. Faster motor cars are also associated with dangers. The development of fast, cheap and comfortable air travel has had its own disasters, for example the early Comet explosions and two fatal accidents with the DC 10. Processed foods have poisoned as well as nourished. Many modern industrial processes have been found to involve unexpected risks for the work force not least of which has been carcinogenesis. It is probably true to say that in no field of human endeavour has there been entirely beneficial progress without some human casualties in its path.

Against the background of that statement, the first point to be made is that all safety is relative, and on the whole – despite technological progress, or indeed because of it – the world is infinitely safer than a century ago. Human life was considered cheap in the early nineteenth century, and hardship and disability were commonplace. It is only since the commonplace risks of Victorian days have been largely eliminated that the new relatively rare hazards associated with 20th Century technology have been thrown into sharp relief.

Secondly, however, the recent improvements in the quality of life and the reduction in tragedy and suffering cannot be used as an excuse for continuing to accept the remaining risks. People, and politicians in particular, are right to press for the highest possible standards of safety and wellbeing.

In this sequence of argument it is, however, the third point which is the essential one. This is the obvious statement that measures to ensure wellbeing should not be counterproductive. They should not so inhibit progress that benefits are foregone in striving to reach the chimera of zero risk and absolute wellbeing. The world is a real place and

30 *Pharmaceutical Journal*, 223, 6030, 49, 14 July (1979).

not a Utopia. Some balance between progress and risk must be accepted if the greatest good is to be achieved.

This paper has tried to spell out the benefits of modern medicines and to catalogue and classify their risks. However, the underlying fact is that in the present state of the art of therapeutics there is inadequate basic information on which to construct an optimal policy. Manufacturers, prescribers, academics and government regulatory bodies are all to some extent working in the dark in trying to get useful new medicines into clinical practice as soon as possible, while at the same time minimising the risk that they may do harm as well as good. Here there is no nice convenient model that one can put on to a computer programmed to spell out a policy for maximum wellbeing.

There is, however, a strong and growing suspicion that in the past few years the balance has moved the wrong way. Overshadowed by the earlier thalidomide tragedy, and further shaded by the experience with practolol, there has been a fertile climate for those who have sought to publicise the dangers of modern medicines. In turn, governments and their regulatory bodies have been influenced into adopting an attitude of great caution, which may now be against the public interest.

It seems largley to have been forgotten that the pharmaceutical innovator himself has the strongest motive to ensure the safety of his new medicines. At the least, it is commercially disastrous to introduce an unsafe medicine. More importantly, scientists and businessmen in industry are no less responsible as human beings than civil servants or academic scientists. Policies based on the mistaken assumption that industrialists will act ruthlessly and recklessly are just as misguided as those which suppose that government administrators and advisers have nothing but altruistric motives. By imposing unnecessary bureaucracy and insisting on undue caution the regulatory bodies can do at least as much harm as the over-enthusiastic industrial innovator. It becomes potentially damaging to technology when industrial innovation is suspect and bureaucratic caution is praiseworthy.

Thus it is important first to look at the balance between the responsibility taken by the pharmaceutical companies and that taken by the government regulatory bodies. The latter have perhaps been too slow to recognise that they are there as a backstop and not as a frontrunner in setting standards for the quality, efficacy and safety of new medicines. In practice, new safety tests are invariably devised in industry rather than by administrators. The danger is that by unimaginatively demanding the inappropriate application of these test procedures, the regulatory bodies may have been stifling valuable innovation. There seems to have been a relentless process of accretion in the tests expected on new medicines. One manufacturer thinks a particular procedure may be relevant – although he probably has no evidence for this – and the new test is then demanded from all. There probably needs to be a fundamental reappraisal of what is now expected before a new medicine can be tried in man or introduced on to the market.

There is also the question of the balance between the academic advisory Committees and the Civil Servants in the Department of Health itself. Since the original setting up of the Committee on Safety of Drugs in 1964, there has tended to be a shift towards putting more responsibility on the part-time Committees although the Civil Servants can themselves give approval for the start of clinical trials if they choose to accept this responsibility. In practice, all such decisions are now referred to the Expert Committee. In this paper it has been argued that the decision to start closely supervised clinical trials represents a relatively minor risk. Fortunately the decision to start trials is one which government has recently recognised should be taken as expeditiously as possible.

Finally, there is the question of product liability. The recommendations of the Pearson Commission would have the effect of imposing legal as well as moral responsibility on a company for any of its products which inadvertently did harm. This will tip the balance still further towards an excessive emphasis on safety at the expense of overall progress. There needs at least to be some safeguard for the manufacturer if 'strict liability' is to be introduced. The best solution having regard to all the problems involved, not just unforeseen side effects but also those arising despite proper warnings having been given, would be the establishment of a centrally financed scheme under the National Health Service which would evaluate claims and make compensation payments where appropriate on an objective basis without regard to the particular financial strength or size of the company which manufactured the product. Under such a scheme the fund would be reimbursed by the pharmaceutical company concerned after the event where it could be shown that it had been negligent. Failing this, there should be an upper limit placed on the liability of any one company with the Government providing a back-up assurance in case that limit is exceeded. Obtaining insurance for the strict liability risk, even within a

reasonable limit, will nevertheless be extremely difficult.

Going back to take the broad view, it must be clear from this paper that the question of balance in ensuring reasonable safety of new medicines is a difficult one. Already many steps have been taken to avoid adverse reactions, and new measures are at present under discussion. In this debate, it is important to see the matter in perspective. The objective can never be absolute safety. In the light of the contribution of new medicines so far, there must be proper consideration given to the importance of continued pharmaceutical innovation. There must be a recognition that such progress must continue to involve risks. Such risks must be taken if the benefits of future new medicines are to be made available to the professions and the public. They must be seen in perspective not only against the enormous benefits which modern medicines have brought, but also against the risks which are considered reasonable and acceptable both in other fields of medicine and in life as a whole.

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