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The Office of Health Economics was invited to make a contribution to the celebration of the Golden Jubilee of the ABPI. This booklet is our response. In it we have broadly surveyed British pharmaceutical progress through the last fifty years. We have had to do so within limits of space and time which have constrained our text in two main aspects. First, we have chronicled the development of new medicines by way of groupings related to the illnesses they attack. Second, we have not pursued any analysis of costs, prices, benefits or risks which find a place in our usual studies. The booklet is written as a history of achievement in pharmacology which deserves to be commemorated at this Jubilee.

Stemming also from the constraints is another editorial decision. The pharmaceutical industry is a great international industry. Very many developments for the benefit of medicine have come from overseas, principally the United States, Germany and Switzerland. And from these countries also have come very substantial industrial involvement in Britain.* Nevertheless, the reader will find that it is only in the case of certain medicines developed by British-owned companies that the innovators have been identified by name. We decided to limit attributions in this way because it seemed to me that it would be appropriate to be frankly British on this British Jubilee. But we so decided well knowing that the whole is greater than its parts, and that the British firms make up but one part of the truly international pharmaceutical industry in this country.

**A list of ABPI Member companies appears on page 58.*

A fiftieth anniversary invites some retrospection. Fifty years ago the British pharmaceutical industry formed the Wholesale Drug Trade Association, which became in 1948 the Association of the British Pharmaceutical Industry. This change of name in the late 1940s occurred against a background of unprecedented advance in the research, development and manufacture of pharmaceutical products which was radically altering the practice of medicine. It marked the emergence of a highly scientific research-based industry which has subsequently become one of the most prosperous sectors of the British economy.

The industry had in fact been starting to take shape before the 1930s, being involved particularly in the production of anti-toxins and certain vitamins. One of the principal factors involved at this early stage of development was the wider use of the active ingredients of crude drugs which made it logical for a number of one-time 'chemists and druggists' to develop into bulk manufacturing-wholesalers. At the same time the increasing complexity of manufacture forced many local dispensing pharmacists to relinquish their role as makers of medicines: the mixtures, powders and hand rolled pills traditionally prepared in the back of the dispensary were gradually being replaced by compressed tablets and bulk mixtures more appropriately produced in the large manufacturing plants of wholesale druggists. In addition, developments in organic chemistry and particularly in the synthesis of dyes encouraged a number of manufacturing concerns at one time exclusively involved in these activities to diversify into the field of pharmaceuticals. But it was not until the years succeeding 1935, when the first of the sulphonamides was introduced, that advances in chemo-therapy drew together the strands of earlier origins and brought about an acceleration of development to create the pharmaceutical industry structure with which we are familiar today.

Over the last 50 years an entirely new *materia medica* has emerged from the discoveries by scientists working in academic centres and in the research laboratories of the pharmaceutical industry. But it has been the exclusive

responsibility of the industry to develop the means of producing these new medicines on a commercially viable and large enough scale to make them available to doctors everywhere. It therefore seems appropriate to take the opportunity afforded by the Golden Jubilee of the Association of the British Pharmaceutical Industry to give some account of the major advances that have been achieved in chemotherapy during the last fifty years. The performance of the pharmaceutical industry in terms of innovative success, industrial development and contribution to the British economy has been matched by few other industries over this period of time.

The true origins of the chemotherapeutic revolution lie in the experimental studies conducted by Ehrlich during the early years of the twentieth century. In his work with dyes and histological specimens he noticed that different cells and specific parts of certain cells showed a selective staining effect and he conceived the idea that dyes might be used to deliver chemical substances to various parts of the body. In 1906 he thus wrote:

'In order to use chemotherapy successfully we must search for substances which have an affinity for the cells of the parasites and a power of killing them greater than the damage such substances cause to the organism itself, so that the destruction of the parasite will be possible without seriously hurting the organism. This means we must strike the parasite and the parasites only, if possible, and to do this we must learn to aim with chemical substances.'[1]

Experimental work had already produced valuable antiseptics but they could only be used externally. Nevertheless inorganic arsenic had been shown to clear trypanosomes from the blood of infected horses and an organic arsenical had been used successfully on man. This inspired Ehrlich to make and test further compounds. After screening more than 600 substances his efforts resulted in the discovery of arsphenamine (Salvarsan) which attacked the spirochaete of syphilis within the body without harming the host. It was soon followed by neoarsphenamine (Neosalvarsan) which was widely used until 1945 when it was superseded by penicillin.

Although the search for other chemotherapeutic 'magic bullets' continued, nearly a generation was to elapse before the 'take-off' into the modern era of sustained progress occurred. In this interval there were nevertheless a few notable advances. Insulin, for example, was added to the limited range of medicines capable of attacking causes (which included quinine for malaria, emetine from ipecacuanha for amoebic dysentry, digitalis for certain heart conditions, vitamins C and D for scurvy and rickets respectively and mercury and salvarsan for syphilis).

1 Marquardt M (1949). Paul Ehrlich. Heinemann.

PAUL EHRLICH (1854-1915)
(By courtesy of the Wellcome Trustees)

Fundamentally, however, chemotherapy was still largely concerned with providing symptomatic relief rather than cure and was based on tinctures, syrups and remedies which were often blunderbuss in character. According to the British Pharmacopoea of 1932 there were just 36 synthetic drugs, including aspirin, phenacetin and barbitone, all of which had been developed in Germany before 1900.

Then in 1935 came the breakthrough. The successors of Ehrlich, similarly imbued with the belief that the strong affinity of aniline dyes for bacterial protoplasm could be turned to beneficial account, continued to test vast numbers of dye compounds for signs of an ability to protect against infection. Certain dyes, such as gentian violet and methylene blue were shown to be active against bacteria in artificial culture, but they had little or no effect on infections in the experimental animal in non-toxic concentrations. Eventually, however, success was found in a new azo dye giving a brick red colour which was fast for wool. It was called Prontosil and was shown to protect mice against a lethal inoculum of haemolytic streptococci. Clinical confirmation of its action in erysipelas and other infections was obtained before full announcement of the discovery was made early in 1935 by Domagk in Germany and by Horlein at a meeting at the Royal Society of Medicine in London.

Within a few months French scientists demonstrated that the chemotherapeutic effect of Prontosil was not attributable to its dye properties but to its breakdown in the body to sulphanilamide. This immediately generated a massive effort by many industrial research laboratories to obtain derivatives of sulphanilamide with improved properties. Thousands of compounds were made and one of the earlier successes was sulphapyridine (the famous M & B 693) which had outstanding effects on pneumococcal pneumonia and whose therapeutic virtues were extolled by Sir Winston Churchill following a bout of pneumonia in December 1943: 'This admirable M & B, from which I did not suffer any inconvenience, was used at the earliest moment and, after a week's fever, the intruders were repulsed'. Subsequently pharmaceutical research within the industry has produced sulphonamide products with increased potency, lower toxicity and a wider spectrum of action and examples of those in common use today are sulphadiazine, sulphadimidine, sulpha-

thiazole and a synergistic combination of sulphamethoxazole and trimethoprim.

In many ways, looking back over the last 50 years, the discovery of the sulphonamides was the outstanding therapeutic advance which revolutionised attitudes to pharmaceutical progress. For the first time streptococcal infection became amenable to treatment. Mortality rates for puerperal fever (infection of the genital tract after childbirth), perhaps the worst manifestation of this type of bacterial infection, fell immediately the sulphonamide drugs became available. In England and Wales in the twenties and early thirties deaths from this cause – most fatal infections being streptococcal – numbered about 1,000 per annum. Today it is an extremely rare cause of death.

The sulphonamides were also the first drugs to be effective in cerebro-spinal meningitis and septicaemia, both of which could prove fatal in young persons. Lord Platt has recalled the case of a young doctor who was brought into hospital with an acute staphylococcal septicaemia which had developed after he had squeezed a small boil in his nose.[2] In the absence of any treatment he died in five days. Finally, many large hospitals have records showing the loss of medical personnel who died following infection acquired, via a finger prick or scratch, while attending a septic patient. Today acute local infections can so easily be arrested that the stage of septicaemia need never be reached.

The therapeutic benefits of the sulphonamides have not been restricted to their antibacterial activity. At an early stage of clinical use it was noticed that some of the products had a blood sugar lowering effect, similar to that of insulin. This led to the development of carbutamide and tolbutamide, oral therapy for late onset diabetes. Another important therapeutic development stemming from the sulphonamides was the discovery that some compounds had a powerful diuretic action. Further research led to the introduction of chlorothiazide which has subsequently been employed widely in a variety of diseases in which disturbance of water and electrolyte metabolism are prominent.

At the same time, the development of the sulphonamides had a major impact on the metamorphosis of the

2 'Private and Controversial'. Lord Platt. Cassell, London.

pharmaceutical industry. It heralded the beginning of an era based on large scale high precision manufacturing techniques and companies became involved in capital outlays far beyond anything they had ever had to contemplate in earlier phases of development. It also demonstrated the commercial hazards inherent in a research intensive industry: the advent of sulphonamides rendered serum therapy for pneumonia obsolete overnight.

PENICILLIN

In 1928, seven years before Domagk announced his discovery, Sir Alexander Fleming whilst studying staphylococcal variants found that one of his culture plates was contaminated with a fungus which destroyed surrounding bacterial colonies.[3] He investigated further the properties of 'mould broth filtrates' which, for brevity, he named 'penicillin' and found that the latter, in concentrations three times as strong as carbolic acid, could dispose of germs without any harmful effects. Fleming used the broth from the mould as dressings for surface infections such as boils and styes. However, the substance was unstable, losing its effectiveness very quickly and as anti-septics of well-established value were available there was little to commend the new substance from a clinical point of view. This factor combined with the difficulty of preparing enough for experiments caused it to be put aside as a curiosity.

Ten years later, and in a 'medical climate' which the introduction of the sulphonamides had made responsive to the idea that germs were no longer inaccessible within the human body, Sir Ernst Chain and Lord Florey, in Oxford, decided to undertake a systematic study of antibacterial substances produced by moulds and bacteria which exhibited unusual chemical and biological properties. Eventually, their work led to the isolation of penicillin in the form of a brown

3 Serendipity played an important role in the discovery of penicillin. The famous original plate could not have been produced had it been incubated in the manner in which Fleming probably intended. Instead it lay on the laboratory bench whilst he was away on holiday, at a time in the previously hot summer of 1928 when the temperature fell to levels assuring the necessary respective growth rates of the staphylococcus and the penicillium.

powder which had high antibacterial activity, yet proved non-toxic to mice. With this powder Fleming's earlier results were substantiated and moreover it was shown that injections of these penicillin preparations were able to cure animals of severe general infections caused by several strains of highly pathogenic bacteria; in the absence of penicillin treatment none of the animals survived.

The first 'mass production' apparatus consisted of a set of milk churns, a dog-bath, a stirrup-pump and a milk cooler borrowed from a dairy. The moulds were grown in milk bottles. The broth was brewed in East London and transported to Oxford in milk churns. Then in February 1941 an opportunity presented itself to evaluate the curative potential of penicillin in humans. A policeman was critically ill with septicaemia in Oxford's Radcliffe Infirmary. Sulphonamides had proved ineffective and in a final attempt to save his life it was decided to use the small stock of penicillin that had been extracted from 100 litres of broth. Immediately the man's temperature dropped and his general condition continued to improve until the meagre stock of penicillin was used up. Then he relapsed and died. Later when more penicillin had been manufactured a series of dramatic cures was achieved and it became clear that if the medicine could be mass produced it would have profound implications for the treatment of the war-wounded.

The problem was how to produce penicillin in sufficient quantities. A number of British pharmaceutical firms undertook production by surface culture, at that time the only known method, and agreed to pool their knowledge and experience. But the production techniques were cumbersome: at one factory penicillin mould was being harvested from the surface of 300,000 flasks of broth and at another over a million milk bottles were in continuous use. In these early days of the war, Britain was unable to divert resources to investigating large-scale methods of manufacture. Accordingly, the responsibility for further progress was undertaken by the United States which had not yet entered the hostilities. The work of a drug company with many years of experience in the microbiological production of citric acid and the American government research laboratories soon resulted in the development of better culture methods and large quantities of the medicine became

available, playing an important part in the war effort.

Penicillin provided an effective treatment for syphilis and it soon replaced the sulphonamides as the drug of choice in lobar pneumonia. The latter attacked all ages indiscriminately and was responsible for many premature deaths (Figure 1). 'A fit man in the prime of life, with a wife and young children dependent on him would go to work feeling perfectly well. In the middle of the afternoon, he would be seized with a headache. An hour or so later, he would be feeling so ill that he would have to go home. A week, sometimes only 48 hours, later he would be dead. In different epidemics the mortality rate ranged from 5 to 20 per cent. And there was nothing, apart from giving, at most, marginal help, that we could do for our patients save try and sustain their strength until the crisis occurred in a week or ten days time.'[4]

Lobar pneumonia in a previously healthy person no longer carries the risk nor causes the distress that it did, with the anxious wait for the 'crisis' when the fever dropped dramatically as the immune responses of the body at last killed the invading bacteria. Today, about half of the cases treated with penicillin have a normal temperature within 12 to 36 hours and the remainder within 4 days.

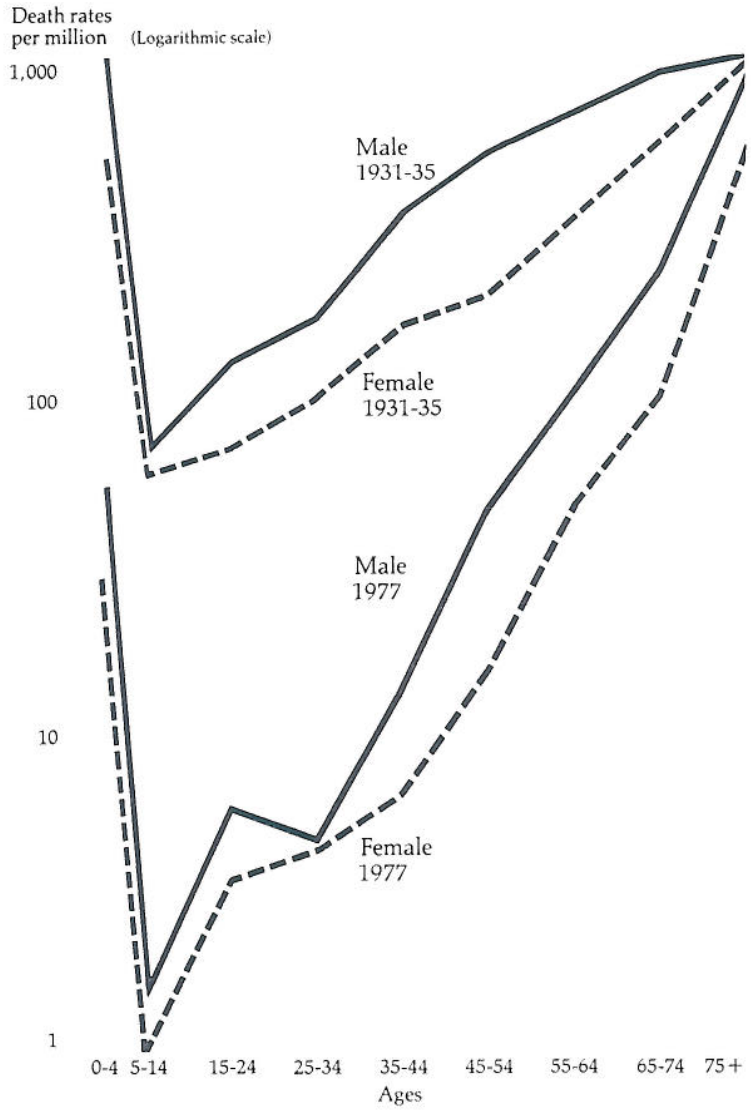
STREPTOMYCIN

The sulpha drugs were not the *therapia sterilisans magna*, the universal germkillers, for which Ehrlich had hoped. They were mainly effective against meningococci, gonococci, haemolytic streptococci and pneumococci, but they had no effect at all on the organisms causing syphilis, tuberculosis, typhoid fever and many other infectious diseases. Penicillin was dramatically effective against other bacteria but it too did not affect tuberculosis. In 1944 however Professor Waksman of Rutgers University showed that cultures of the newly isolated micro-organism *streptomyces griseus* produced a powerful chemotherapeutic action against gram-negative bacilli and, more importantly, against the tubercle bacillus. By the end of the year the activity of the new drug against tuberculosis organisms had been demonstrated and,

4 Sir Harold Himsworth quoted in The Medicine You Take by Lawrence D R and Black J W. Fontana.

FIGURE 1

Lobar pneumonia death rates by age and sex, England and Wales, 1931/35 and 1977.



although the antibiotic was available in only small amounts, clinical trials began.

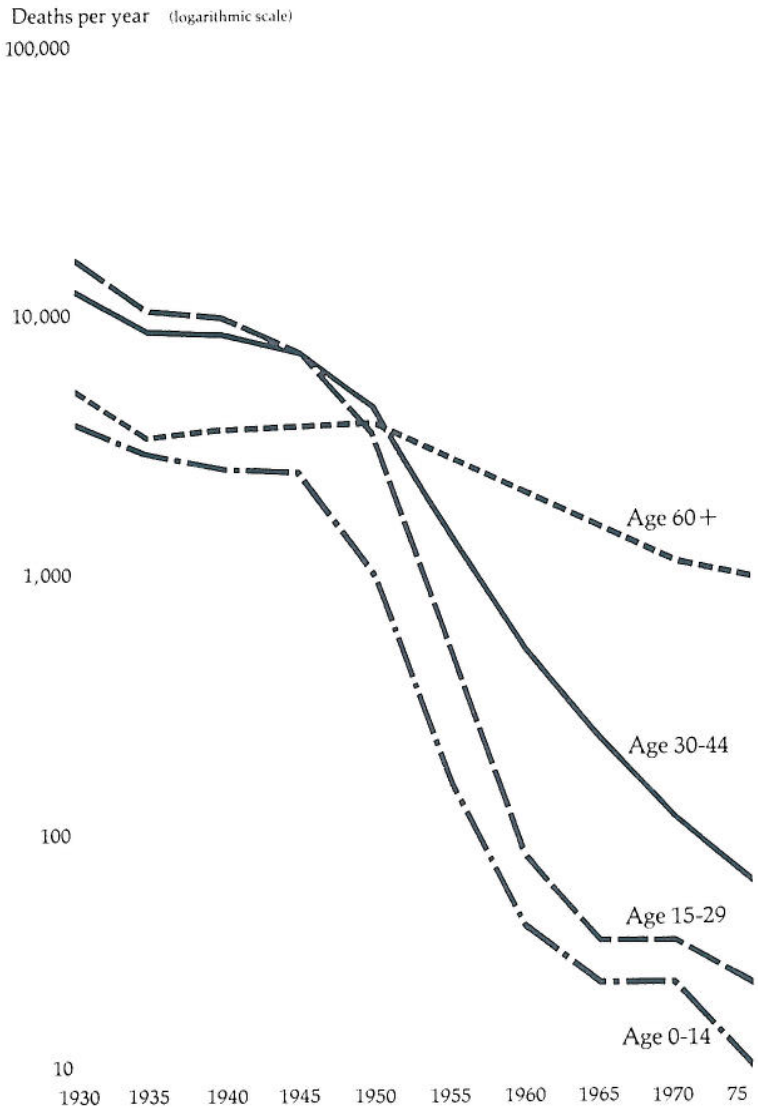
It was soon realised however that the improvement produced by streptomycin alone was frequently only transient: after about six weeks of treatment patients began to relapse because of the emergence of strains of tubercle bacilli resistant to the drug. Nevertheless hopes were again raised in 1946 when Lehmann, a Swedish biochemist, demonstrated that para-aminosalicylic acid (PAS) had a marked activity against the tubercle bacillus both in the test tube and in experimentally infected animals. Subsequently clinical studies both in Sweden and the UK showed that PAS also had a beneficial effect in patients with various forms of tuberculosis. Then trials conducted by the Medical Research Council indicated that streptomycin and PAS employed together constituted a more effective method of attacking tuberculosis than the use of either drug in isolation and, further, that the development of drug resistance was greatly delayed. Thus once industrial research had uncovered an effective and economic means of producing the newer of the two drugs, combined PAS and streptomycin became standard therapeutic practice for tuberculosis and a steady fall in mortality from the disease resulted.

In 1952 isoniazid, a third antituberculosis drug, was discovered. Clinical trials, again under the auspices of the Medical Research Council, soon confirmed its activity but, as with streptomycin and PAS, there was the serious limitation that the tubercle bacillus quickly developed resistance to it. Additional research showed, however, that when isoniazid was used in combination with streptomycin or PAS, resistance could be avoided or at least greatly delayed.

Together these three drugs have made a substantial contribution to the reduction in mortality caused by the 'Captain of the Men of Death' as Milton described tuberculosis in the seventeeth century. The decline in mortality from 1900 to 1945 proceeded at about 3 per cent per year in Britain. With the introduction of effective drugs this annual reduction suddenly improved to 15 per cent and by 1960 the death rate was less than one-tenth that of 1940. Figure 2 indicates that the falls in mortality have been most significant among the younger age groups.

FIGURE 2

Deaths from tuberculosis by age groups, England and Wales, 1930-1975.



ADDITIONAL ANTIBACTERIAL DRUGS

The search for further chemical means of halting bacterial infections was intensified during the 1940s and 1950s and was undertaken principally in industrial laboratories. (The exhaustive nature of the screening programmes is illustrated by the discovery of antibacterial substances in the anal gland secretion of the Argentine ant and in the faeces of blow-fly larvae!) The outcome was a whole range of new and valuable chemotherapeutic agents. Chloramphenicol – the pure crystalline form of *streptomyces venezuelae* which was originally found in a soil sample collected in Venezuela – was discovered in 1948. Industry based microbiologists showed that it was effective against an unusually broad range of microbes, with particular efficacy in the treatment of typhus and typhoid; it is also a valuable therapeutic agent in superficial eye and ear infections.

The first tetracycline to be discovered (from mould growth) was chlortetracycline in 1948. In 1950 this was followed by oxytetracycline and in 1959 a synthetic derivative, demethylchlortetracycline, was introduced. The tetracyclines – so called because of their four ring chemical structure – interfere with bacterial growth (unlike penicillins which damage the developing cell walls of multiplying bacteria causing them to die) and have the broadest spectrum activity against bacteria of any antibiotic.

The macrolides, of which erythromcycin and oleandamycin are examples, are bacteriostatic agents which are active against a narrow group of bacteria similar to those sensitive to the natural penicillins. Consequently they are of value in treating tissue infections resistant to the latter or patients allergic to penicillin. A number of antibiotics have antifungal effects and two examples in common use are nystatin and griseofulvin. The latter, which is particularly effective against ringworm, was first isolated at the London School of Hygiene and Tropical Medicine in 1939. Yet like penicillin its therapeutic potential was only realised years later – in the 1950s in this instance as a result of research and development work by two British pharmaceutical companies, Glaxo and ICI.

In the latter half of the 1950s another chapter in the penicillin story was started, as a consequence of the collaboration between Chain and the Beecham company. By

FIGURE 3a

Mortality by cause, age and sex, England and Wales, 1931.

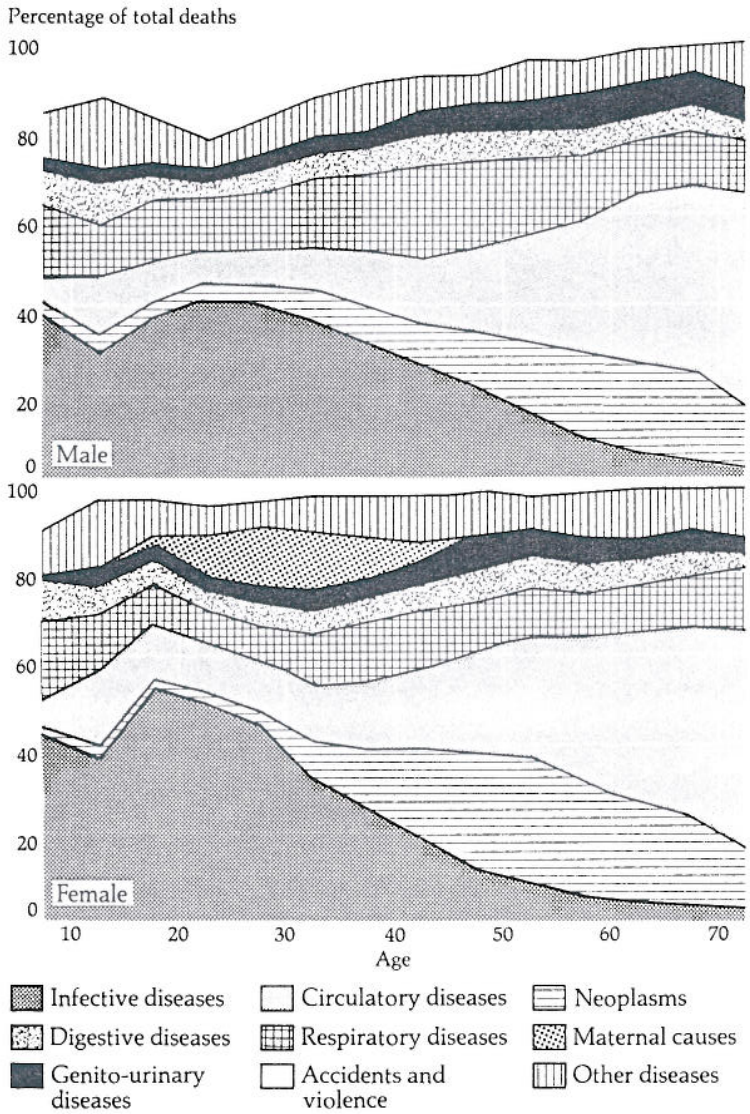
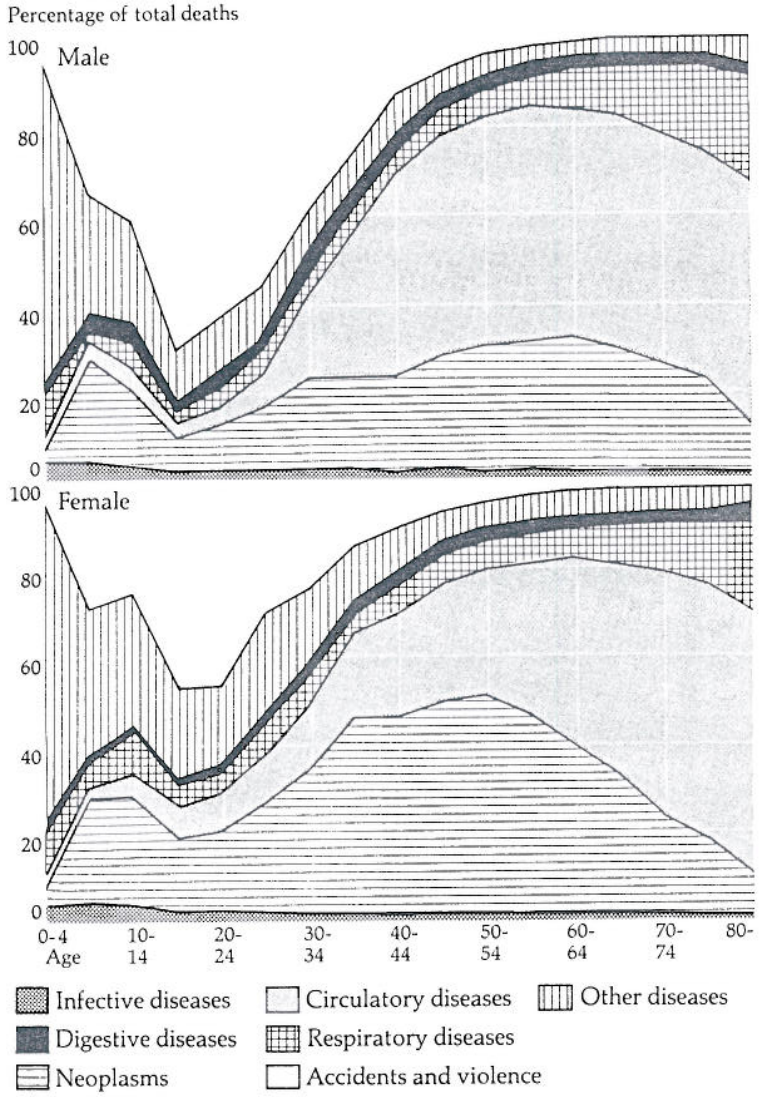


FIGURE 3b

Mortality by cause, age and sex, England and Wales, 1977.



this time it was realised that all the available antibiotic compounds had limitations of one kind or another. The sulpha drugs, chloramphenicol, streptomycin and the tetracyclines all produced in a few patients undesirable side effects and penicillin G and V, though safe and widely used, were ineffective against many bacteria. Moreover the widespread use of penicillin had been increasingly accompanied by problems of drug resistance. The need, therefore, was for new compounds which would combine the safety of the original medicines with a different spectrum of antibacterial activity.

The major advance came in 1957 with the isolation of the basic core of penicillin, 6-aminopenicillanic acid which was eventually obtained in pure crystalline form. This was the starting point for the creation of a new range of penicillins – by attaching different side chains to the nucleus it became possible to produce compounds having activity against many organisms which were beyond the reach of the original penicillins.

The first of the semi-synthetic penicillins – phenethicillin – appeared on the market in the autumn of 1959. Its main therapeutic advantage over penicillin V was that it achieved a higher antibiotic concentration in the blood. But the real potential of the nucleus discovery was demonstrated in 1960 with the introduction of methicillin, the first of the new compounds to be effective against previously penicillin-resistant strains of staphylococci. A year later came ampicillin, active against a wide range of bacteria which were untouched by earlier penicillins and without the side effects of broad spectrum antibiotics outside the penicillin family. Subsequent investigation of several thousand semi-synthetic penicillins has yielded further advances: amoxycillin, for example, while having the same broad spectrum of activity as ampicillin, achieves much higher levels in the blood and is more rapid in its antibacterial effect.

It is difficult both to isolate and quantify the benefits accruing from chemotherapeutic advance over the last 50 years but perhaps those associated with the development of antibacterial medicines present fewer problems than many other areas of medical progress. The most striking feature of this period has been the disappearance of infectious disease as a major cause of mortality (Figures 3a and 3b) and

FIGURE 4a

Expectation of life at selected ages for males, England and Wales, 1871-1976.

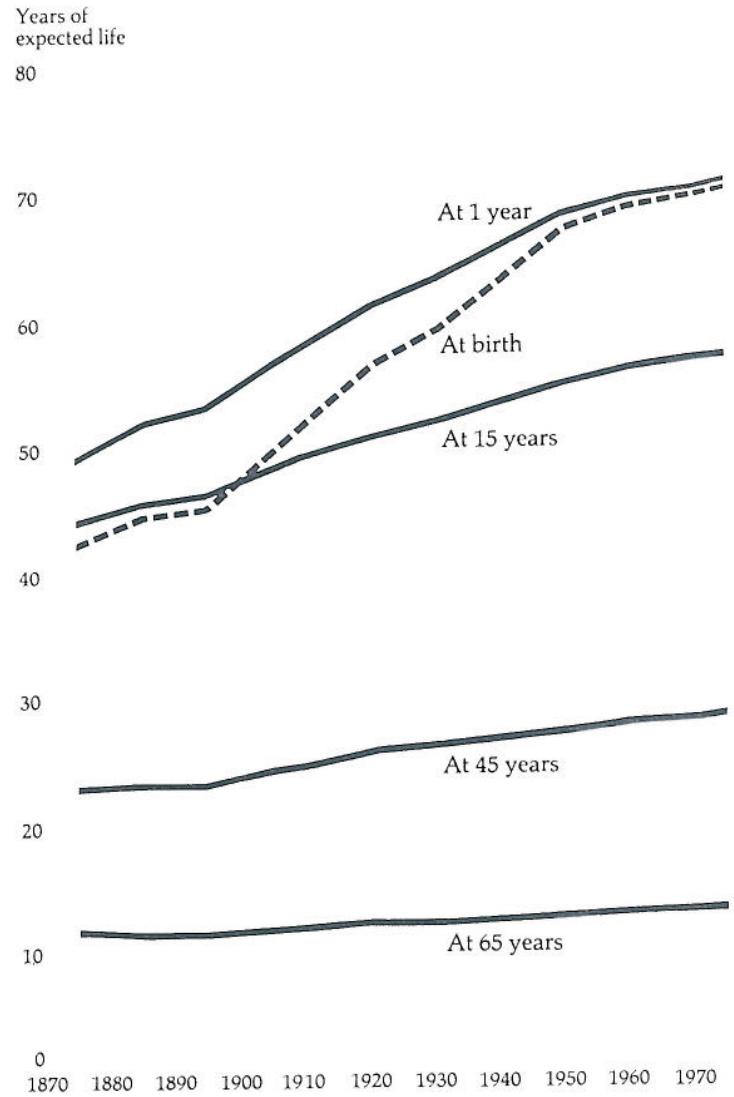
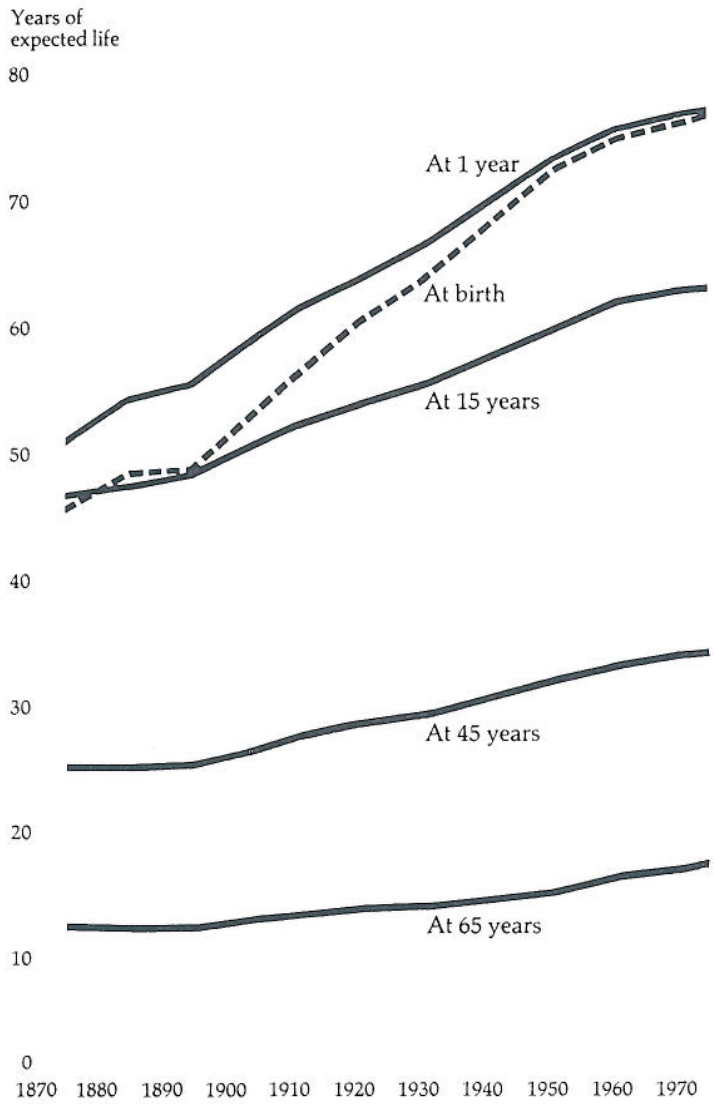


FIGURE 4b

Expectation of life at selected ages for females, England and Wales, 1871-1976.



antibiotics have played an important role in this changing pattern. Improvement has been most marked among children and young adults and has made a major contribution to the extensions of life expectancy shown in Figures 4a and 4b. It should not however be forgotten that the antibiotics have also provided cures for many painful and inconvenient conditions which do not necessarily threaten life; these include otitis, tonsillitis, conjunctivitis, cellulitis, gonorrhoea and cystitis.

Reflecting on these developments, Professor Dollery in his recent Rock Carling Monograph[5] commented that 'some of the early achievements in the treatment of infections were so miraculous as almost to surpass belief. They, literally, changed the world. The watch and wait while the pneumonia of a young adult progressed through crisis to lysis or death. The agony of a child with acute otitis media, or worse still, osteomyelitis. The long-drawn-vigil of the patient with pulmonary tuberculosis coughing away his life. Antibacterial chemotherapy made the cure of such scourges almost a matter of routine'.

By the 1950s the therapeutic revolution was thus well and truly under way and an extensive armoury of antibacterial agents had been established. During the last 30 years the pace of advance has been sustained and effective medicines are now available for an enormous range of human illnesses. In this second phase of progress, however, the emphasis has tended to shift away from the development of dramatically curative medicines towards those which help to improve the quality of life, frequently through the suppression or alleviation of disease processes for which cures or preventive measures have yet to be found.

STEROIDS

Steroids are one such example. Compound E, cortisone itself, was first isolated in 1935. During the early war years efforts to synthesise the steroids were intensified – inspired partly by the belief that their use was enabling enemy pilots to fly at great altitudes without adverse effects. In spite of the

5 The End of an Age of Optimism. Dollery C. The Nuffield Provincial Hospitals Trust 1978.

lapse of interest when this rumour proved unfounded, sustained collaborative research by Kendall at the Mayo clinic in the United States and industrial scientists led to success in 1948 when the first few grammes of cortisone were produced. The manufacturing method was highly complicated and involved 37 steps but the drug was shown by Hench to have a remarkable therapeutic effect for persons crippled by rheumatoid arthritis and this encouraged industry to seek ways of adapting the complex process to quantity production. Subsequent modifications to the basic cortisone structure, undertaken mostly by the pharmaceutical industry, have led to the evolution of a range of steroidal drugs with greatly improved anti-inflammatory properties, including hydro-cortisone, prednisolone and beclomethasone.

Continued research progress has meant however that the position gained by the corticosteroids alongside the traditional painkillers (for example, aspirin) in the treatment of musculoskeletal disorders such as rheumatoid and osteoarthritis has now been occupied, to varying degrees, by the non-steroidal anti-inflammatory agents one of the most important of which was originally synthesised in the Boots laboratories. These medicines are not only highly effective in reducing pain and stiffness thereby enabling many individuals to lead active lives but they also have considerably fewer unwanted side effects than steroid therapy. And in gout, a rheumatic disease characterised by recurrent attacks of acute pain and swelling of the joints, the development of allopurinol in the Wellcome laboratories in the 1960s represented a major step forward for many patients by facilitating control over serum uric acid levels and hence the development of symptoms.

Steroids are still extremely valuable in the treatment of a number of uncomfortable, annoying and inconvenient diseases of the skin. The chronic inflammatory conditions of eczema and dermatitis for example cannot be cured but their symptomatic treatment has been vastly improved by topical corticosteroids, especially the newer fluorinated versions which offer the possibility of control of at least the most troublesome manifestations. In conjunction with antihistamines, antibacterial and antifungal agents, corticosteroids now enable family doctors to treat effectively and quickly many skin diseases that fifty years ago could only be

referred, often without much hope of success, to the specialist dermatologist.

Steroid preparations, such as prednisone and prednisolone, are also employed in the treatment of both acute and chronic asthma. They are almost always indicated in very severe life threatening asthmatic episodes. In the chronic form of the disease the development of steroid preparations delivered by pressurised aerosol has had a major impact on the day to day management of symptoms. Only very small doses of these drugs (beclomethasone dipropionate or betamethasone valerate) are required and they are particularly beneficial in permitting a reduction in the intake of oral corticosteroids. In addition to their alleviative and prophylactic properties, corticosteroids have also been found to raise or restore some patients' responsiveness to bronchodilator therapy.

[Asthma sufferers of all ages can now manage their disease to a much greater extent than in the past as a result of the development of aerosol corticosteroid and bronchodilator therapy. And these two highly effective and convenient means of control have been joined by disodium chromoglycate. The latter is a prophylactic treatment which inhibits the development of immediate and late asthmatic responses to various stimuli through its action on the mast cells in the lungs. It does this by preventing the release of spasmogens and inflammatory agents which follows the initial antigen antibody reaction. This medicine was developed in the laboratories of Fisons Pharmaceuticals and has stimulated important new lines of investigation throughout the whole field of allergy.]

The use of steroids and their subsequent modifications either alone or in conjunction with other medicines has therefore brought relief to many thousands of people principally by increasing mobility, suppressing unpleasant skin irritations and lessening the fear of asthmatic attacks. But their value in other less prevalent disorders should not be overlooked. As replacement therapy steroids have radically transformed the prognosis for victims of Addison's disease; if left untreated the disorder produces anaemia, general languor or debility, feebleness of the heart's action, irritability of the stomach and a peculiar change of colour in the skin, generally proving fatal within three or four years.

In multiple sclerosis, short term courses of steroid therapy (especially adrenocorticotrophic hormone) appear to have a favourable effect on recent relapses.

PSYCHOTROPIC MEDICINES

The mental illnesses constitute another area in which the pharmaceutical industry has played a major role in the development of therapy and made a substantial contribution to scientific understanding. The discovery of neuroleptics was a by-product of industrial research on antihistamines which showed that certain of these compounds possessed pronounced sedative properties. Subsequent work led, in the early 1950s, to the introduction of the first major tranquilliser, chlorpromazine. The latter belongs to the general family of phenothiazines which along with similar medicines have contributed substantially to the management of acute schizophrenic episodes.

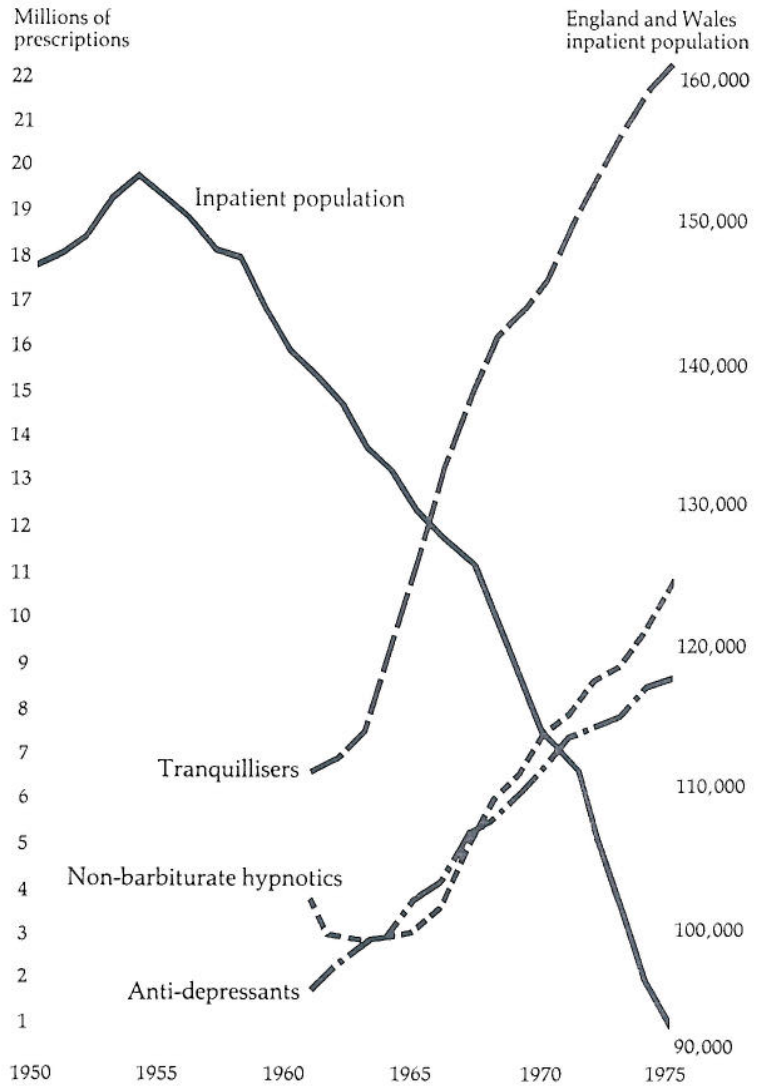
The development of the minor tranquillisers – meprobomate in the 1950s and the benzodiazepines in the following decade – has enabled many thousands of people to function better through periods of potentially disabling anxiety. Pharmaceutical industry investigation in this area has also given rise to an unprecedented acceleration in the understanding of brain chemistry and transmission of nerve impulses.

It was also in the early 1950s that it was first observed that isoniazid, a medicine at that time being used in the treatment of tuberculosis, caused a euphoric reaction amongst many of the people receiving it. Shortly afterwards it was shown that this effect was due to the inhibition of the enzyme monoamine oxidase, the consequence of which was to raise the levels of certain neurotransmitters (e.g. noradrenaline) which in turn gave rise to an antidepressant effect. Monoamine oxidase inhibitors thus became established in the field of psychiatric medicine. In 1957 trials with imipramine, which is similar in structure to the phenothiazines and was originally developed in the hope that it would be effective in treating schizophrenia, showed that it too had an antidepressant effect.

And so by the end of the 1950s there were two groups of antidepressant medicine, the MAOIs and the so-called

FIGURE 5

Prescriptions for psychotropic medicines 1961-1975 and inpatients in mental illness hospitals and units 1950-1975. England and Wales.



tricyclics, available for the treatment of depressive psychoses and, where effective, neuroses. Previously, electro-convulsive therapy was often the only means of relief. These medicines are effective in about three-quarters of the cases of severe depression encountered today. Subsequently there have been further advances in this area, including the use of lithium salts both in the direct treatment of mania and the prophylactic control of manic depression and the introduction of further new types of antidepressants. These generally appear to have a therapeutic action similar to that of the tricyclics coupled with advantages such as reduced side effects or contra-indications and a greater speed of action.

Mental illness hospital data reflect the development of psychotropic medicines (Figure 5). The size of the inpatient population was increasing until the mid-1950s when these medicines became available and since then there has been a steady decline. Psychotropic medicines have catalysed this changing pattern in a number of ways: for example the major tranquillisers have made the treatment of schizophrenia in the community a viable alternative to hospital care for growing numbers of patients. More fundamentally, however, the availability of these medicines has generated enlightened attitudes to psychiatric illness running counter to the institutional approach to care prevailing 30 years ago. Today, most people in psychiatric hospitals are either short stay patients receiving active, and usually successful, treatment or they are psychogeriatric patients over the age of 65 years suffering from irreversible conditions such as dementia and requiring extensive supervision not available elsewhere.

MEDICINES FOR CENTRAL NERVOUS SYSTEM DISORDERS

There have been a number of major advances in the treatment of disorders of the central nervous system. A good example is provided by Parkinsonism which involves progressive muscular rigidity and tremors and affects between sixty and eighty thousand elderly people in the United Kingdom. The precise cause of Parkinsonism is as yet unknown and no preventative or curative agent so far exists. Research has however led to the development of a pharmacological means of alleviating the principal symptoms. The drug is called levodopa and is considered to be among the most important advances in neurology.

Levodopa (or L-Dopa) was first isolated in 1913 but it was not until the 1960s that the potential value of the chemical in the treatment of Parkinsonism became recognised. Research had shown that in the brain the levels of a naturally occurring neurotransmitter called dopamine were markedly reduced in individuals suffering from Parkinson's disease and it was theorised that this deficit could be associated with the muscular disability characteristic of the disease.

Attempts to use dopamine itself to treat Parkinson's disease proved unsuccessful because of its inability to pass from the blood into the brain. It was then discovered that its chemical precursor, levodopa, not only penetrated the so-called blood-brain barrier, but was also converted into dopamine within the brain. Thus an effective symptomatic treatment for Parkinsonism became available. Subsequent work has led to the availability of products combining L-Dopa with compounds which not only reduce unwanted side effects such as nausea but also prevent the breakdown of L-Dopa.

Epilepsy is another central nervous system disorder with symptoms which are generally responsive to drug therapy. Idiopathic epilepsy (that is, occurring in the absence of any recognised abnormality) is the most common type and is characterised by fits and convulsions of varying degrees of severity. Although some epileptics die from cardiac arrest sustained due to hypoxia in *status epilepticus* the main burden of epilepsy is not due to shortening of life expectancy but to the miserable insecurity (not to mention risk of injury) inherent in the sudden and largely unpredictable loss of motor control.

Although there is no cure for epilepsy it has become increasingly possible to control symptoms. Phenobarbitone has been used since the 1910s and phenytoin was discovered in the 1930s. Subsequently numerous anti-epileptic drugs have been introduced following a search for substances which reduce excessive stimulation in the brain without depressing vital centres or inducing drowsiness. The availability of a choice of chemotherapeutic agents coupled with a better understanding of how best to employ them in

the treatment of epilepsy means that for 75 per cent of epileptics it is now possible to reduce substantially the frequency of fits and even to eliminate them.

ANAESTHESIA

A discussion of the central nervous system could not be complete without mention of the revolutionary contribution of pharmacological advance to anaesthesia and hence to surgery. At the same time developments in this field have been an important factor in the emergence of the anaesthetist as a specialist practitioner in his own right. Anaesthetists are now an essential part of the medical team with a function extending well beyond the surgical procedure itself, particularly involving the pre-operative preparation and post-operative care of the patient.

In the 1920s anaesthesia was a matter of an ether and chloroform drop bottle, an open mask, mouth gag and tongue forceps; there were no muscle relaxants; no blood readily available for transfusion; continuous intravenous drips were unknown until 1935. Then from the 1930s progress began to be achieved. Intravenous induction by means of a barbiturate, first hexobarbitone and later thiopentone, provided a means of avoiding the often stormy and unpleasant journey from consciousness to full anaesthesia experienced with the traditional inhalation agents. The problem of providing sufficient abdominal relaxation but only at the expense of deep states of anaesthesia giving rise to considerable post-operative morbidity was resolved in 1942 by the introduction of curare. Today muscle relaxants used as adjuncts to anaesthesia are of two types; the blocking agents such as tubocurarine chloride which interrupt neuromuscular transmission by competing with acetyl-choline for receptor sites and depolarising agents such as suxamethonium chloride which act by rendering the tissues incapable of responding to the transmitter. Generally, the former, by virtue of a more prolonged action, are used in major operations while the latter with a much shorter effect are employed in minor procedures or manipulations and for intubation.

Developments have been wide ranging and have of course included the evolution of more effective and safer general

inhalational anaesthetic agents. Halothane, for example, was first used in 1956 and has since been employed extensively throughout the world proving to be a major advance on older anaesthetics. If unconsciousness is not required adequate conditions for a number of surgical procedures can be obtained with local anaesthetic techniques which have advanced considerably since the introduction of cocaine into medical practice by Koller in 1884. Local anaesthetics act by preventing the transmission of impulses along nerve fibres and at nerve endings and are of two chemical types: the older and less stable ester compounds such as amethocaine and procaine and the more recently developed amides which include lignocaine and cinchocaine. An alternative technique involves the use of certain synthetic morphine-like analgesics with a major tranquilliser to produce neuroleptanalgesia, a state of calm mental detachment with mild sedation accompanied by a high degree of analgesia, which enables a number of surgical and manipulative procedures to be undertaken with the co-operation of the patient.

The pharmacological developments of the last 50 years have therefore made available to the anaesthetist of today a wide range of products from which may be chosen a combination of agents to create the appropriate surgical condition for each one of the two and a half million operations performed in England and Wales each year.

MEDICINES AND RECEPTORS

The origins of much recent therapeutic advance can be traced back to the physiological and pharmacological studies undertaken by Sir Henry Dale at the Wellcome Research Laboratories in the early years of the present century. His investigations with an extract of ergot led to the discovery of histamine and acetylcholine thereby preparing the way for a revolution in pharmacology. Indeed Dale had a central role in establishing the chemical explanation of nervous transmission. When impules travel along the nerve fibre which pass between brain and muscles, they release, at the end of the nerve, the contents of millions of tiny vesicles, each of them having contained a few thousand molecules of acetylcholine. These molecules of acetylcholine convey the 'information' from nerve ending to muscle fibre and initiate

its contraction. Today it is known that there are many, perhaps thousands, of chemical regulators which orchestrate the activities of the millions of cells in the body. These natural chemicals lock on to the appropriate receptors which are located on the cells and trigger off some predetermined change in cellular activity. In theory these receptors provide a site at which synthetically manufactured chemicals could act to restore the normal functioning which is lost in a number of common illnesses.

Knowledge of the potential therapeutic significance of receptor sites has been put to valuable use in angina with the development of beta blocking drugs such as propranolol. In angina, pain (sometimes severe) is experienced when the heart is stimulated by, for example, excitement or exercise, because the coronary arteries fail to deliver enough blood and oxygen to match the needs of the heart's greater workrate. Confronted by the inability effectively to increase oxygen supply by drugs, researchers decided to look for means of preventing noradrenaline (the heart-stimulating chemical released during exercise, etc) acting on the heart as a way of controlling the latter's demand for oxygen.

The search led to drugs like propranolol. The latter is recognised and bound by the heart's noradrenaline receptors but not only does it fail itself to trigger the usual changes in enzyme activity but also, by occupying the receptor, prevents noradrenaline from doing so. Propranolol was found to have an additional property of crucial importance. The noradrenaline receptors in blood vessels differ from those in the heart and propranolol appears to be an antagonist of only the adrenoceptors found in the heart. Consequently, propranolol interferes with the changes in the heart resulting from stimulation without significantly interfering with the nervous control of the blood vessels. During exercise, therefore, the noradrenaline-secreting nerves which supply blood vessels continue to shunt the blood away from skin and abdominal organs and increase the supply to the muscles.

When patients with coronary artery disease are treated with propanolol they are able to do more work without pain and there is also evidence that long-term blockade of beta-adrenoceptors increases life-expectancy. An unexpected

bonus has been the clinical finding that propranolol is an effective treatment for hypertension.

The latter, commonly known as high blood pressure, is a cause for concern because it increases the likelihood of illness and premature mortality in affected individuals as a result of its effect on the brain, heart and kidneys. In the most severe (malignant) cases, before effective treatment became available in the 1950s, 90 per cent of patients died within a year of diagnosis; the new drugs immediately halved this mortality.

The medicines used to treat high blood pressure are complex chemicals with many quite distinct actions. Like beta blockers some of the following antihypertensives have derived from a growing understanding of the role of chemicals and receptors in different cells: adrenergic nerve blocking drugs such as guanethidine; alpha receptor blocking drugs which act on nerve receptors in artery walls, blocking excitatory impulses and thus causing the blood vessels to dilate; methyldopa which interferes with the production and action of substances in the body which act on blood vessels to raise the blood pressure; and rauwolfia alkaloids and related compounds (e.g. reserpine) which deplete the tissue, brain and nerve ending stores of chemicals having a similar effect. Finally, the diuretics – the first major one of which was chlorothiazide which became available in 1958 – have an important role in the management of hypertension because of their ability to promote fluid excretion.

Asthma sufferers have also benefited from greater scientific understanding of the role of chemical receptors. During the 1960s isoprenaline was extensively used to relax bronchospasm, that is to open up the airways. The drug achieves this by stimulating the beta 2 receptors of the bronchial smooth muscle. Unfortunately at the same time isoprenaline also stimulates the beta 1 receptors of the heart, increasing its forcefulness and rate of contraction. Extensive research did nevertheless uncover the solution to this problem – the currently widely used longer acting selective beta 2 bronchodilators, such as salbutamol and terbutaline.

Investigations in this general field have also led to the development of therapy for some of the less prevalent disorders, for example, myasthenia gravis. The latter, which only affects between two and four individuals per 100,000

population, commonly begins in early adult life and is characterised by weakness and fatiguability of skeletal muscle. It is the result of a decrease in the number of functioning acetylcholine receptors at the postsynaptic membrane which causes a disruption in the normal transmission of nerve impulses. Consequently, although an initial movement may be normal, repeated movements rapidly become weak and the patient may be unable to co-ordinate the eyes, walk, or in severe cases, even breathe. The discovery of neostigmine was therefore a dramatic event for the victims of the disease. This drug prevents the normally rapid destruction of the chemical transmitter acetylcholine released at the endings of the nerves that supply the muscles, thus prolonging its effect and maintaining neuronal connection.

Finally, a major advance in the treatment of stomach ulcers has been achieved in the last few years and this too has centred on a better understanding of chemical regulators. Ulcers resulting from excess stomach acid can be extremely painful and debilitating; 'one is not altogether fit for the battle of life who is engaged in a perpetual contention with his dinner' wrote Meredith in the nineteenth century. More dramatically, they may lead to the serious, even lethal complications of severe bleeding or perforation when the stomach contents leak into the peritoneal space and cause peritonitis. In many such cases unpleasant major surgery may be required even though it carries a not inconsiderable fatality rate.

Until recently ulcer therapy had been strictly limited: antacids provide only symptomatic relief and atropine in doses sufficient to reduce acid secretion (through its effect as a competitive antagonist to acetylcholine) has unpleasant effects such as blurred vision and trouble in emptying the bladder. However, besides acetylcholine two other substances are found in the stomach which are powerful stimulants of gastric secretion – histamine and gastrin – and following a ten year pharmaceutical industry research programme cimetidine has now been developed which suppresses both these substances by selectively blocking certain histamine receptors.

Although yet to be fully evaluated over long term usage this new medicine offers many patients the possibility of

rapid healing of their ulcers and for those more severely affected the hope of avoiding potentially dangerous abdominal surgery.

REPLACEMENT CHEMOTHERAPY

The effect of many of the therapeutic advances outlined above has been to raise the quality of life for large numbers of people, generally without major impact in terms of extending life expectancy. However, diabetes is a disease in which the benefits of therapy have been of both types. This disorder is characterised by a deficiency or diminished effectiveness of insulin, a hormone produced by the pancreas and responsible for lowering the blood sugar level by encouraging the burning up of sugar in the tissues to produce energy. A standard medical text in 1907 stated that 'diabetes is in all cases a grave disease and the subjects are regarded by all assurance companies as uninsurable lives: life seems to hang by a thread, a thread often cut by a very trifling accident'. Indeed the acute, severe form in young people was usually fatal within a few months or at most two years. Although the initial breakthrough came with the discovery and isolation of insulin by Banting and Best in the 1920s, the industry has over the past 30 years developed more versatile and purer injectable insulins and have supplemented these with a range of oral preparations. The benefits of these advances coupled with the use of antibiotics for complications, can be seen in appropriate mortality data: among those aged 15 years or less, for example, the diabetic death rate fell from 10 per million population in the 1930s to 2 per million in the 1970s.

Pernicious anaemia, a condition in which the body is unable to absorb vitamin B_{12} from food resulting in a fatal incapacity to form red blood cells, is another example of successful replacement therapy. Until 1926 it remained an incurable condition. But then Minot and Murphy discovered that patients could control their disease by following an unpleasant dietary regime requiring the consumption of half a pound of raw liver each day. Two years later it was discovered how the unknown antipernicious anaemia factor could be extracted from liver and pharmaceutical companies became involved in producing these extracts. At first the

preparations were crude and had to be taken by mouth at frequent intervals but, with continued research, purified and concentrated forms were developed which required much less frequent administration and could be given by injection, in relatively small amounts.

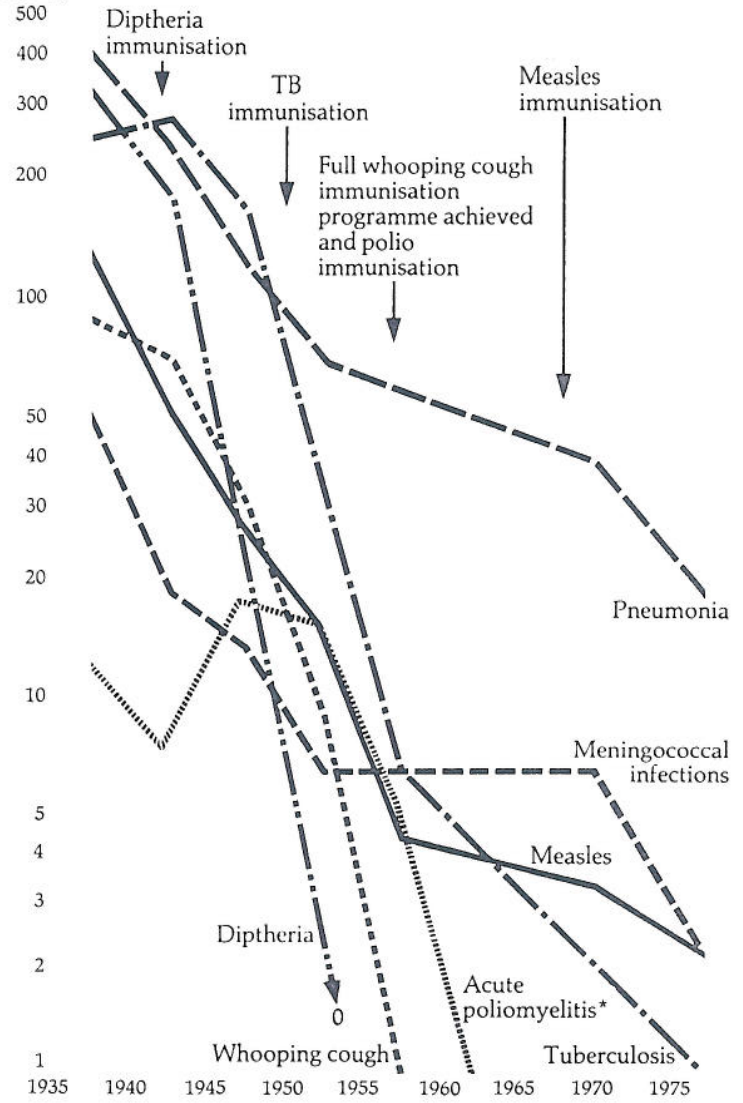
Research then became focused on attempts at isolating the still unknown factor from liver extract and developing a pure substance. Success was achieved in 1948 with two research teams, one British and one American, both involving pharmaceutical industry scientists, announcing their findings within a few weeks of each other. The discovery of vitamin B_{12}, as the anti-pernicious anaemia factor was later named, has meant that for a fatal disease there has been substituted the slight inconvenience of an injection every third month.

This section has looked at some of the principal advances in chemotherapy over the last 50 years. There have been many others: no detailed mention has been made of oral contraception and its value in avoiding the unhappiness and stress associated with unwanted pregnancy; of diagnostic agents; of the development of analgesic compounds facilitating control over pain ranging from minor discomfort to extreme distress; of yet further advances in antibacterial chemotherapy including the cephalosporins which have a broad spectrum of activity and in certain conditions avoid the problems of resistance confronting some of the older drugs in use; and of vaccination which, in conjunction with antibiotics and the improvements in nutrition, hygiene and other social factors, has played an important part in driving home the attack on childhood disease – death rates for those aged 1-14 years have fallen from over 3,000 per million living in 1931-35 to 327 in 1977 (Figures 6 and 7).

The overall result of all this progress is that medicine and the pattern of disease of 1980 would be virtually unrecognisable to the physician of 1930. Most hospitals for tuberculosis have been shut, and many wards for infectious diseases, which often used to be located in separate buildings away from the main 'clean' surgical wards, have been closed or given over to the care of old people. Young persons between the ages of 15 and 25 relatively seldom die from disease today – nearly 58 per cent of mortality in this age group stems from accidents, poisonings and violence and within the latter group accidents on the roads account for

FIGURE 6

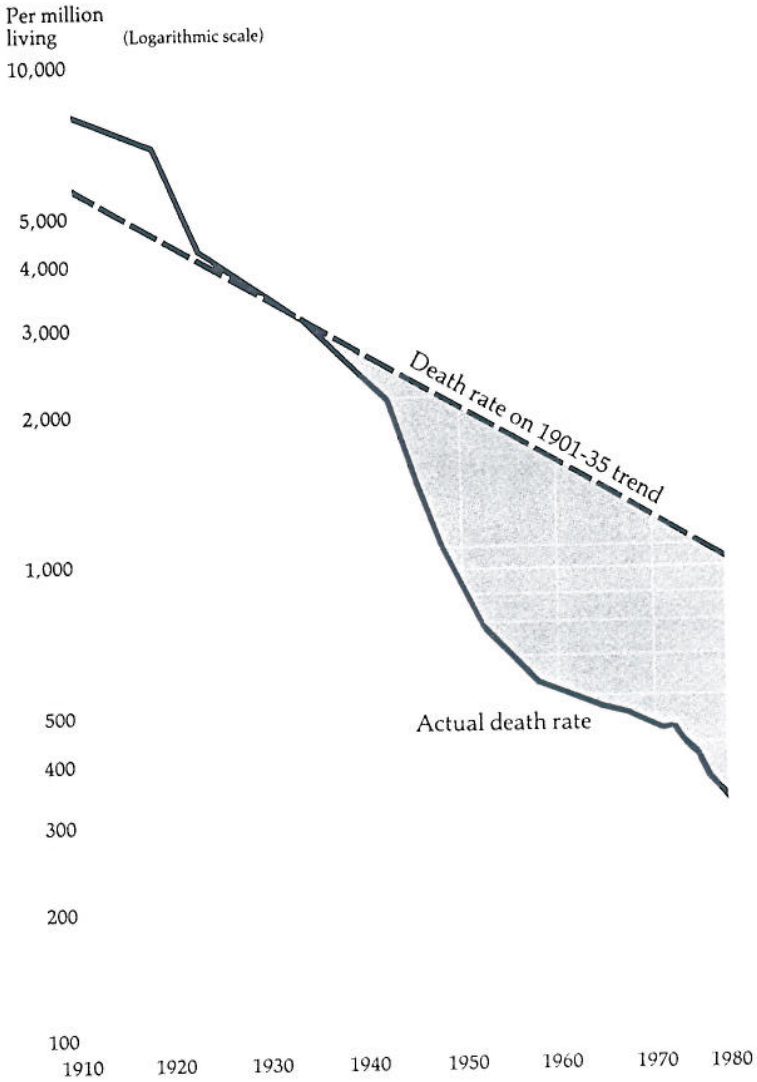
Childhood (ages 1-14 years) deaths by selected causes. Death rates per million living, England and Wales, 1931/35 to 1977.



*Death rate for acute poliomyelitis embraces all children under 15 years.

FIGURE 7

Children aged 1-14, death rate per million living. England and Wales. Five yearly averages 1911/15-1961/65. Annual rates 1966-1977.



68 per cent of deaths. The atmosphere and length of stay in mental hospitals have improved considerably as a result of the use of modern psychotropic drugs. The great modern advances in surgery have only been made possible by the developments in anaesthesia and chemotherapy. Beds on medical wards in general hospitals are now mostly occupied by patients suffering from what might be called the natural processes of ageing – various forms of atherosclerosis of the cerebral, coronary and renal arteries – requiring little or no acute medical attention.

All medicines available to the prescribing doctor today have been developed for use by the pharmaceutical industry and a great number of these have in fact originated from the latter's own research endeavours. Innovation is the life blood of the modern industry and as the current Secretary of State for Social Services, The Rt Hon Patrick Jenkin, has recently commented, without it 'the industry would be bound in the end to wither and die'.[6] Consequently huge sums are spent on research and development. It is estimated that in 1978 the industry spent £190 million (that is more than 10 per cent of turnover) on this activity. This represents a substantial increase over the £29 million recorded in 1970 (Table 1). Inflation must of course be taken into account but even when this is done R and D expenditure demonstrated a real growth of more than two and a half fold between 1970 and 1978.

New pharmaceutical products are sought in a variety of ways. A long-established method, employed since the beginning of pharmacology, involves the collection of botanical, animal and microbial material which is then subjected to techniques of extraction and purification to obtain the active pharmacological agent. But with the advent

TABLE 1. *Research and development expenditure by the British pharmaceutical industry.*

Year	*£m*	*Year*	*£m*
1960	7.5	1970*	29.0
1961	7.8	1971*	35.0
1962	8.3	1972*	41.9
1963	na	1973	44.1
1964	10.4	1974	50.0
1965	11.6	1975*	82.6
1966	13.0	1976*	120.0
1967	16.4	1977*	150.0
1968	18.9	1978*	190.0
1969	24.2		

*Estimated

6 IMS Pharmaceutical Marketletter, 17 September 1979.

of synthetic compounds and a low yield factor this procedure has been less prominent since the 1950s. In the past valuable new remedies have also resulted from serendipity (penicillin for example) or have been derived on the basis of a fallacious hypothesis: Minot and Murphy introduced liver for the treatment of pernicious anaemia because dogs they had rendered anaemic by repeated bleedings were found to recover more rapidly on a diet of liver than on any other foodstuff; this was because of liver's very high iron content which had nothing to do with its ability to convert a megaloblastic into a normoblastic bone marrow. In other instances therapeutic advance has stemmed from the observation and exploitation of unexpected side effects accompanying the use of already established drugs: the thiazide diuretics, tranquillisers and antidepressants were developed in this manner.

Modern day innovation, however, is much more dependent upon highly sophisticated and comprehensive research programmes of one type or another. Some medicines have stemmed from research with a specific planned objective in view. The discovery of the beta blockers for heart disease and cimetidine for peptic ulcers may be regarded as successful examples of deliberately targeted research programmes within the industry.

In many other instances drug innovation has been achieved by altering the molecular structure of preparations with a recognised pharmacological action to produce drugs of enhanced activity, less toxicity and greater convenience in use than the originals. This method of drug development has been criticised for introducing numerous preparations differing insignificantly from each other and called by a large number of brand names. However, such 'me too' drugs – as they are often disparagingly called – should not be denigrated for, just as motor cars and other modern appliances have gradually evolved from slight changes on earlier models over the years, so these new medicines generally constitute useful improvements on their originals and may be disproportionately beneficial for particular groups of patients. Although the outcome of the modification process need not necessarily represent a great advance in terms of chemical novelty this method of innovation is widely recognised as an empirical technique that is both sound and effective and one

which requires considerable imaginative skill and experience in moving systematically from parent-compound to new drug. Any pressure to reduce this kind of industrial research because of notions of repetition and 'me-tooism' would be positively detrimental for it would deprive society of one of the best means of obtaining maximally effective medication.

Possibly two of the best known examples of this means of drug innovation are provided by steroids and antibiotics. In the former case, once cortisone had been synthesised (1944) and shown to be effective in rheumatoid arthritis (1949) the problem to be overcome was its tendency to retain sodium and, with it, intravascular fluid. This was achieved in 1954 with the development by a pharmaceutical company of a potent glucocorticoid with much less salt-retaining effect – prednisone. The latter differs from cortisone merely by virtue of having an additional double bond in the 'A' ring. This characteristic was discovered through trial and error, through the testing of an endless series of modified and substituted sterol rings until the desired effect was achieved and as Hench, the Nobel Prize winner in Physiology and Medicine, has commented 'if the pharmaceutical chemist were not to bother with minor modifications on the drawing board, we might have missed some of the most amazing, hopeful cortisones that have ever been discovered'.[7] Fortunately, as the field of steroids developed, the pharmaceutical industry became increasingly active in devising techniques of synthesis and the overwhelming majority of synthetic steroid drugs of today have their origins in commercial laboratories.

Many antibiotics have been developed from a base antibiotic which itself may have had little clinical value. For example, rifamycin B was unstable, but the later development, rifampicin, is a valuable antitubercular drug; cephalosporin C was clinically useless but potency was vastly increased with cephalothin and oral dosage possible with cephalexin. In the aminoglycoside field neomycin led to kanamycin with greater safety which in turn led to gentamicin with a broader spectrum of activity and increased efficacy.

Focusing on diuretics some critics of the molecular modification approach to drug evolution might have suggested that further products were unnecessary once chlorothiazide had been developed. Nevertheless the subsequent arrival of frusemide represented a significant advance – it became a mainstay in the treatment of acute congestive heart failure. Its rapid speed of action meant that patients who in the past have required rotating tourniquets and actual withdrawal of blood to produce an immediate drop in blood volume could be treated with a single injection. Ampicillin, diazepam and the modern oral contraceptives are yet further examples of valuable therapeutic advance through processes of molecular adjustment.

Screening programmes are another method widely used in the development of new drugs. New chemicals and organisms, evolved either by synthesis in the laboratory or by investigation of naturally occurring substances, are subjected to a network of screens employing several different species of animal. Computer analysis of recorded non-response as well as change provides an 'activity profile' which then facilitates the selection of compounds for more detailed pharmacological and other forms of scientific study.

In a typical programme of drug development a chemical of potential therapeutic interest would then undergo tests such as LD 50 (determining the dose fatal to 50 per cent of a test animal population) to give initial indications of the therapeutic and toxic dose ranges. These would be followed by intermediate term toxicity investigations in two or more animal species and pharmacokinetic and pharmacodynamic studies.

Once these are completed and the results analysed (healthy) volunteer studies are commenced in order to establish as soon as possible whether the absorption, distribution and metabolism of a drug are similar in man to the pattern shown in test animals. These studies will then influence the choice of species for long-term toxicity testing.

Following the volunteer study stage, chronic toxicity (at least two species), fertility, teratology and perinatal studies are conducted, normally simultaneously. In many cases carcinogenicity tests are also made over an extended period. Only after this stage is a clinical trial certificate normally granted. Trials may then proceed on patients, under the strict supervision of specialists. Their duration and detail depends on the nature, function and intended use of the

7 US House of Representatives, Hearings before the Anti-Trust and Monopoly Sub-Committee, 1961-62.

medicine concerned. It is on the results of these investigations that, perhaps eight or ten years after the original tests for therapeutic activity and at a total cost now estimated at between £20 million and £30 million, a product licence permitting release of the new medicine to the market may be granted.

THE FUTURE

In this year of the Association of the British Pharmaceutical Industry's Golden Jubilee, member companies (totalling 154 in 1979 and producing between 95 and 99 per cent by value of the industry's annual turnover) can justifiably be proud of their pre-eminent role in the evolution of chemotherapy over the last 50 years. And it is to be hoped that the industry can maintain its innovative momentum during the next 50 years, for not only are there patients for whom relatively slight improvements on existing therapy would generate disproportionately large benefits but, more fundamentally, there are many areas of ill-health where a substantial curative breakthrough has yet to be achieved. This is true of most deep cancers, most atheromatous disease of arteries, mental illnesses such as schizophrenia and dementia and for certain neurological disorders like multiple sclerosis.

It is of course difficult to predict medical advance. For example, in the late 1940s and early 1950s it seemed perfectly feasible that chemotherapy for viruses by extension from antibacterial chemotherapy would appear within a few years but these hopes were not realised. Equally in those times it seemed unlikely that mental diseases, because of their essentially obscure nature, would be brought within the ambit of pharmacological treatment but this has turned out to be one of the most striking examples of modern therapeutic success. Today there are nevertheless firm grounds for optimism concerning the likelihood of substantial progress in the treatment of many forms of ill health.

This is the case with viral infections which have been one of man's most elusive foes. Progress is being achieved on a number of fronts – for example, promising results with drugs attacking the herpes viruses which cause fewer blisters and shingles have been reported in recent years. Research is also

being directed at the development of vaccines to prime the body's natural defence mechanisms to produce protective antibodies against viral infections. One of the major obstacles to progress lies in devising suitable vaccine manufacturing processes and this has stimulated investigation into the potential value of genetic engineering techniques. If bacteria that can readily be grown in huge vats can be made to accept insertions of 'foreign' viral genes as their own, and not only reproduce them but manufacture the proteins coded for those genes, then they could provide the basis for the production of effective, safe and economical vaccines.

Perhaps one of the most exciting prospects for chemotherapeutic advance in this field lies in the development of the interferons. The latter are substances produced in the body as a defence against virus infection and are capable of rendering cells resistant to many different viruses. Understanding of how this resistance is produced is incomplete but at least two mechanisms appear to be involved. Interferons 'set off' a number of enzyme reactions in the cell which can prevent a virus using the cells' protein synthesis machinery for its own reproduction. They can also induce changes in the cell membrane which make it difficult for any virus that has survived the first line of attack to escape from the cell and thus spread the infection.

The discovery of the interferons was first reported in 1957 and the potential therapeutic value of devising successful manufacturing techniques soon became clear. Unfortunately problems in quantity production and purification – arising, inter alia, from the fact that interferon is produced in only minute quantities and is thus difficult to separate from other cellular proteins and because of its species specific nature – have severely inhibited the availability and hence clinical evaluation of interferon. However the involvement of several pharmaceutical companies in explorations of the feasibility of various cell culture techniques and the recent announcement that the gene for human interferon has been successfully cloned in bacteria suggests that sufficient quantities of interferon should soon become available to allow a thorough investigation of the potential that has already been demonstrated in a number of small scale clinical trials.

There is also evidence that interferon may be effective against certain cancers. It slows the division of cancerous cells and improves the responses against them of the body's normal immune system. Although therapeutic advance along these lines lies in the future cytotoxic chemotherapy has already provided a means of effective treatment in a number of cancers. Thus the progress made in the treatment of the leukaemias, of advanced Hodgkin's disease and, to a lesser extent, of the non-Hodgkin lymphomas can largely be attributed to the use of chemotherapy on its own or in combination with radiotherapy. And in some solid tumours there have been similar gains – trophoblastic tumours, testicular tumours and in neuroblastoma and nephroblastoma. It is in the commoner solid tumours of adult life that progress has been less conspicuous: the benefits of chemotherapy are ill-defined and uncertain. Nevertheless vast sums of money have been and continue to be spent on cancer research and investigative results throughout this very wide field offer encouraging signs for future progress although it is unlikely that there will be a single wonder drug or even group of wonder drugs that will do for cancer what the broad spectrum antibiotics have done for bacterial infection.

Research into pain mechanisms and their control has generated new knowledge and raised the possibility of therapeutic advance. The recently discovered peptides – the enkephalins and endorphins – which occur naturally in the brain have been shown to have certain morphine-like and hence analgesic, properties. The precise physiological role of these substances remains to be elucidated: there are, in the central nervous system, several opiate receptors with different pharmacological characteristics – one type of receptor has a higher affinity for naturally occurring enkephalins than for morphine or synthetic analogues, whereas for a second type of receptor the reverse seems to be true. It is possible that one of these peptides – or an analogue – may turn out to have a therapeutic role in the control of pain. Furthermore, the discovery may facilitate the long-standing aim of separating the addictive and analgesic properties of the opiates.

A great deal has also been learnt in the latter part of the 1970s about the way in which platelets adhere to a site of bleeding or other vessel wall damage and the role of

prostacyclin in preventing such aggregation. Knowledge of the delicately balanced mechanisms involved seems certain to mean important developments in the treatment and prevention of intravascular thrombosis.

There is considerable scope for therapeutic advance in many other areas of ill health. Increasing understanding of the mechanism of action of genes at the cellular level for example may lead to the development of drug systems that will intervene in the defective process in a favourable way – phenylketonuria and retinitis pigmentosa may yield to this approach. It also seems likely that the chemotherapy of bacterial disease will continue to improve with more effective and less toxic drugs which have a reduced susceptibility to bacterial resistance becoming available. And the understanding being derived from immunological studies – particularly the nature and interactions of the cell types involved in the immune response – is likely to lead to a much greater ability to manipulate that response in order to alleviate clinical problems such as auto-immunity and those accompanying organ transplantation.

One of the most important methodological developments in the field of immunology over the last few years has been the technique for producing monoclonal antibodies.[8] Most foreign substances (such as viruses, proteins, molecules etc) present several antigenic determinants on their surfaces and when injected into an animal each antigenic determinant can elicit antibodies, each being of several different molecular structures. However, any individual cell contributing antibodies to this mixture produces only one type of antibody; it is one of a clone of cells that eventually dies out. It is now known how to make such antibody-producing cells immortal by fusing them with certain types of tumour cells: single hybrid cells may then be selected and grown in tissue culture (cloned) and still produce antibodies. Because all the cells in a single clone are identical only one molecular species of antibody is produced by the progeny of a cell initiating a clone. Production of an individual antibody in large quantities is thus possible for the first time. The technique, which has already had a substantial impact on research requiring the production of highly specific and uniform

8 Medical Research Council Annual Report 1978-79.

antisera, will lead to the large-scale production of antisera for diagnostic and therapeutic purposes.

Finally, drug delivery systems are continually being improved, raising the therapeutic efficacy of medicines. Surgical implantation of devices such as drug pellets, reservoirs or pumps might have many applications including for example the infusion of agents such as lidocaine for irregular heart rhythms, perhaps triggered in response to the detection of an abnormal rhythm by an implanted pacemaker; the infusion of immunosuppressive drugs to prevent the rejection of transplanted organs; the administration of analgesics for chronic severe pain, and the localized infusion of antibiotics and other drugs.

Liposomes may be an important element in future advances in chemotherapy. They are multi-layer semi-synthetic droplets created ultrasonically out of a mixture of natural oily substances (lipids) and water, which contain a therapeutic agent in solution. By controlling the frequency and energy of the ultrasonics a whole range of droplet sizes and structures can be made to predetermined specifications. Droplets of different characteristics might then be used to deliver therapeutic doses of drugs to specific target organs, in a manner analgous to Ehrlich's original 'magic bullets'. Liposomes could be of significant value in a number of diseases such as leishmaniasis. Furthermore, initial investigations aimed at improving therapies for arthritis have shown that if standard steroid drugs are injected into the joints of experimental animals in the form of liposomes then the dose needed to produce a significant reduction swelling can be 100 times less than if the drug alone is used. They may also have other important medical uses – including a dramatic improvement in the effectiveness of vaccines – as well as a range of uses in biological and pharmacological research: they have the ability to cross cell membranes, thus raising the possibility of investigating the effects of drugs in situations which might otherwise have remained inaccessible.

The potential for therapeutic advance is thus considerable but there will inevitably be limits to what can be achieved. Thus it is unlikely that cells that have 'died' in the sense of losing all function and anatomical integrity can be revived and the gradual failing of cells with age is probably

irreversible (although it might be slowed). But perhaps the major constraint on progress is an economic one. Funds for basic research, undertaken in both academic and industrial laboratories to develop the foundations for new innovations, are limited and the increasing amount of time involved in the development phase (which is almost exclusively the province of the pharmaceutical industry) has meant that the conversion of a new drug to an effective and widely available medicine is an extremely costly process.

Today for every novel chemical entity which becomes established as a useful therapeutic substance, about 10,000 other compounds have been tested and rejected. This identification process, followed by comprehensive testing procedures, development and manufacture requires of a pharmaceutical firm developing a single new medicine an expenditure currently estimated at between £20 million and £30 million. Consequently the number of companies that are able to participate in fundamental research and development activities has diminished over time. Nevertheless, the innovative genius of the industry – reflected in the fact that of the 150 most popularly prescribed drugs in 1977 only 22 were available 31 years earlier – is such that, given adequate research funds, scientific and technical challenges are unlikely to prove insuperable and society can look forward with confidence to the introduction of major new medicines, as well as valuable improvements to existing ones, before the Association of the British Pharmaceutical Industry reaches its centenary.

THE PHARMACEUTICAL INDUSTRY TODAY

From its diverse origins the industry has emerged to become one of the most successful and fastest growing sectors of British manufacturing industry today. In the first half of the 1930s annual output was below £20 million and the £100 million mark was not reached until the beginning of the 1950s. By 1975, however, the value of the industry's output had soared to beyond £1,000 million for the first time. Substantial growth of 74 per cent over the following three years took the total to £1,880 million in 1978. Focusing on the five year period 1973-78 the average growth rate per annum at 1975 prices of pharmaceutical output stood at 6.2 per cent, comparing very favourably with 2.2 per cent for chemicals and negative growth for manufacturing industry as a whole.

The pharmaceutical industry, which employs more than 74,000 people directly and probably provides jobs for about twice that number in feeder industries, continues to be one of the most productive sectors of British industry. Between 1970 and 1976 net output per employee rose by 118 per cent from £4,707 to £10,261.

Analysis of the industry's output in 1978 shows that 35.8 per cent (that is £666 million) of the total value was exported. Setting this figure against the value of pharmaceutical imports in the same year (£227 million) produces a net positive trade balance of £439 million, which is a substantial contribution to the British balance of payments. Furthermore, it is one that has been growing steadily in recent years (Figure 8). The established reputation for quality, safety and reliability of British pharmaceuticals creates demand from all parts of the world. In 1978 Nigeria and West Germany were the leading export markets, together accounting for 15 per cent of the total value of exports (Table 2). Antibiotics of all types, valued at £82 million, were the most important single group of products exported by the British industry.

A further £190 million (10.1 per cent) of the industry's output in 1978 went to the household medicines market and £301 million (16.0 per cent) was divided between domestic sales of veterinary products, inter-company trading and

FIGURE 8

Pharmaceuticals: Exports and imports, 1950-1978.

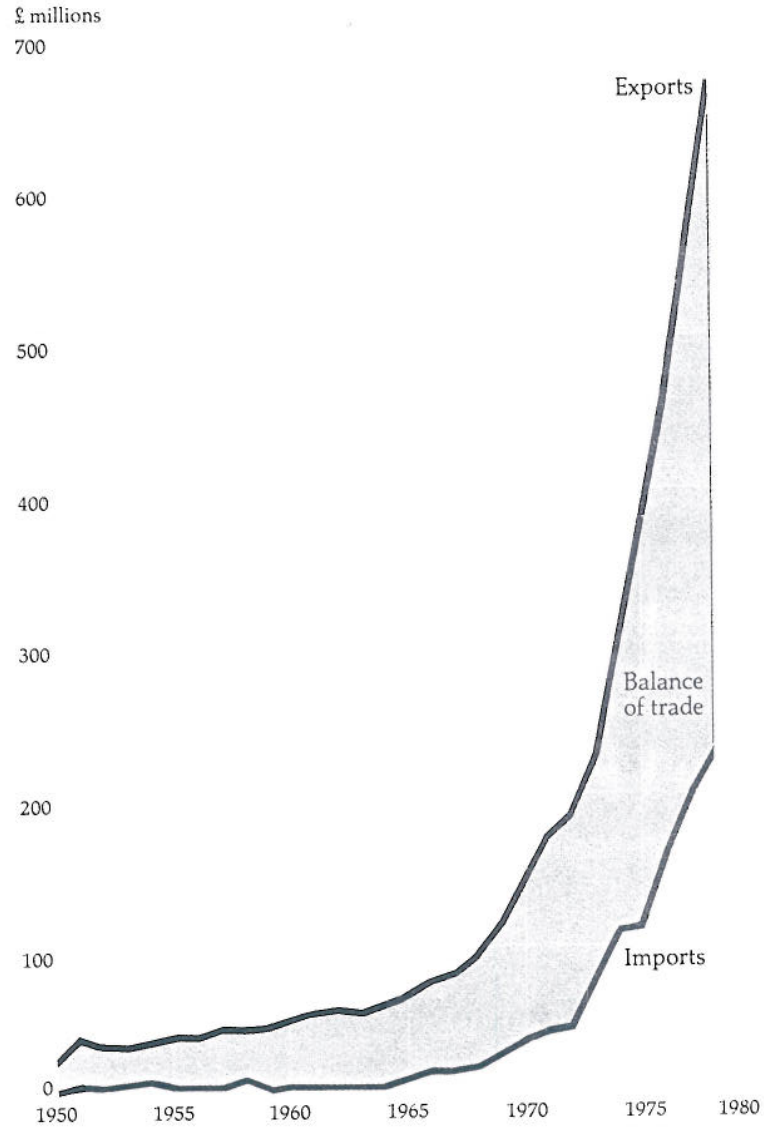


FIGURE 9

Pharmaceutical sales to the NHS, 1967-1978.

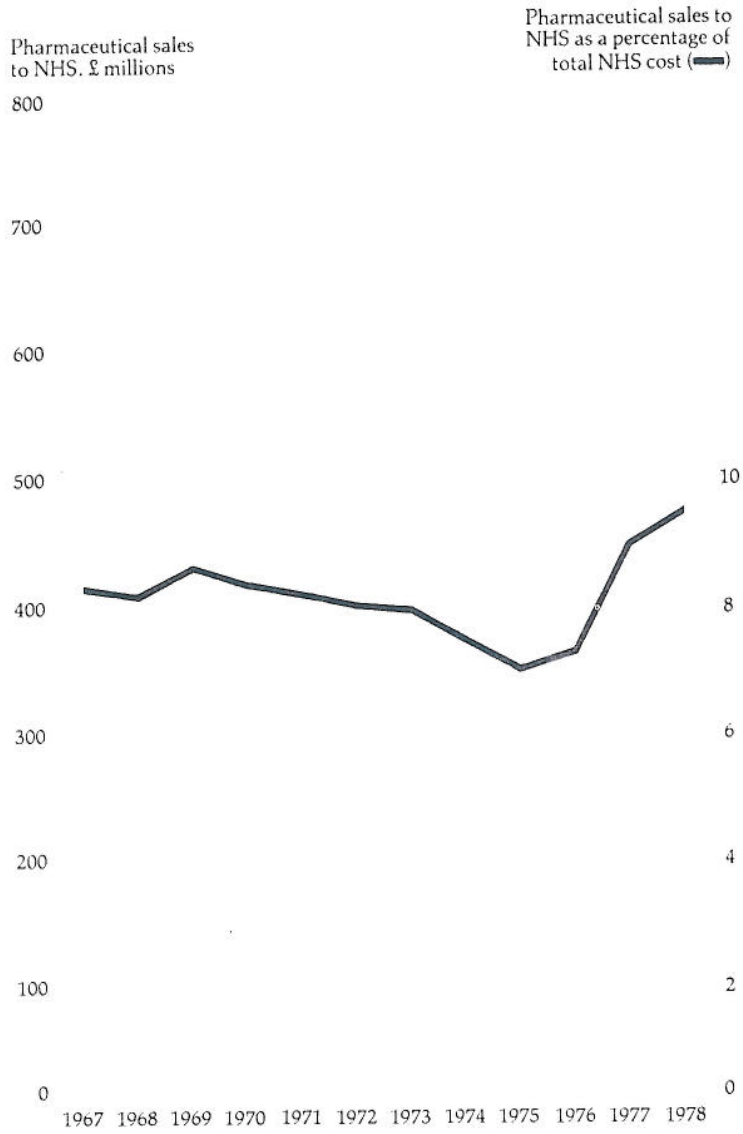


TABLE 2. *Principal markets of UK pharmaceutical exports, £ million.*

	1975	*1978*	*% increase over 1975*
World	378.1	665.7	76
OECD	205.4	387.9	89
Commonwealth	91.1	161.8	78
W. Europe	163.9	299.4	83
EEC	100.7	199.6	98
EFTA	46.1	79.8	73
Latin America	13.3	17.1	29
Nigeria	25.6	51.8	102
W. Germany	17.9	50.0	179
Republic of Ireland	20.5	42.2	105
Italy	18.9	30.9	63
Sweden	16.6	29.7	79
Iran	12.5	29.0	132
Japan	14.4	27.5	91
Belgium	15.9	26.7	68
USA	16.9	21.1	25
France	12.5	19.6	57
Netherlands	7.6	18.6	144
Switzerland	12.4	17.9	44
Denmark	7.2	11.7	63

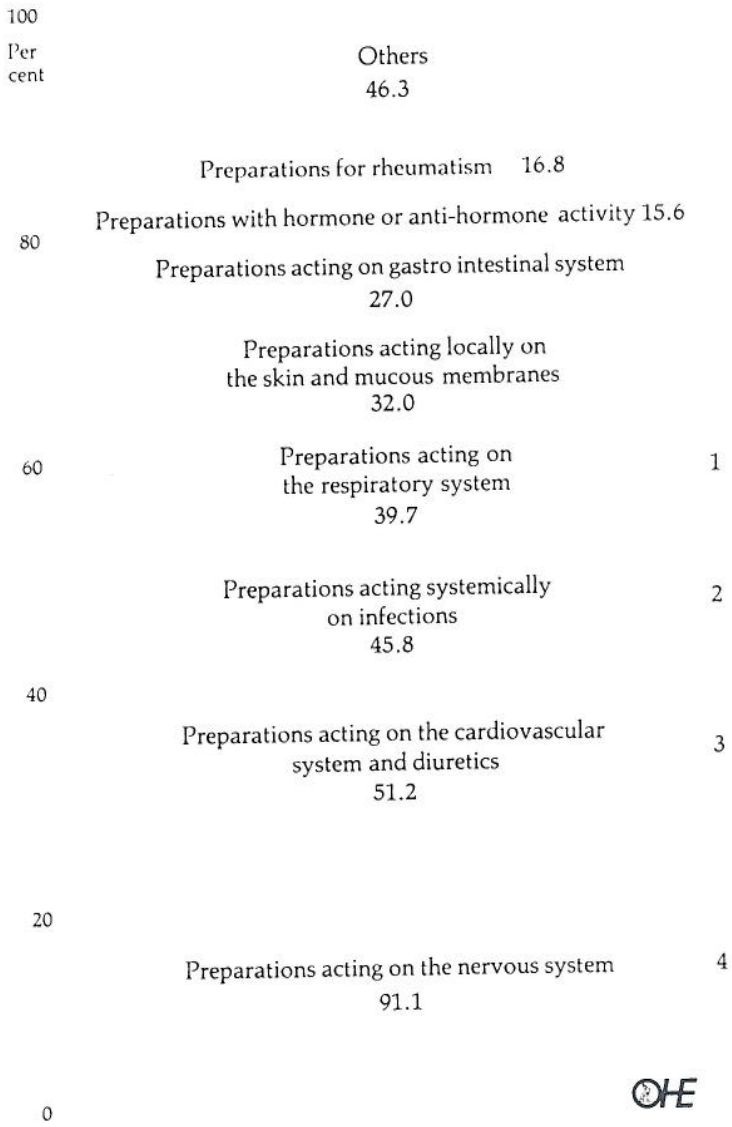
miscellaneous items. The industry's principal market was of course the National Health Service. The latter accounted for £723 million (38.5 per cent) of the industry's output in 1978, only very slightly more than the proportion exported.

More detailed analysis indicates that 80 per cent (£578 million) of this total represented medicines for prescription use by the family practitioner services and 20 per cent (£145 million) was purchased for use by hospitals. Together these two parts of manufacturers' sales to the NHS accounted for 9.3 per cent of total expenditure on the latter in 1978. This proportion of total NHS cost has remained relatively stable in the recent past, never exceeding 10 per cent (Figure 9).

In 1978, a total of 378.1 million prescriptions were written by general practitioners and dispensed by chemists. The most frequently employed of the industry's prescription medicines, estimated in the region of 2,500 branded products or perhaps more than 10 times that number if different formulations and dosage strengths are taken into account,

FIGURE 10

Distribution of prescriptions (millions) by therapeutic class, Great Britain, 1978.



1

Expectorants and cough suppressants

Others

Preparations for asthma

2

Cephalosporins

Sulphonamides

Tetracyclines

Others

3

Penicillins

Diuretics

Preparations acting on the heart

Others

4

Hypnotics

Vaso dilators
Vaso constrictors

Anti-hypertensives

Others

Sedatives and tranquillisers

Major analgesics

Minor analgesics

Anti-depressants

TABLE 3. *Number of prescriptions by selected therapeutic groups, Great Britain, 1967-1977, millions.*

	1967	*1969*	*1971*	*1973*	*1975*	*1977*
All groups	*299.4*	*292.3*	*294.4*	*313.9*	*334.8*	*351.3*
Antacids	12.6	11.0	11.1	11.4	11.2	8.1
Antispasmodics						2.7
Tonics	5.7	4.5	3.6	3.9	4.8	1.4
Gastro-intestinal sedatives						2.8
Preparations acting on the heart	5.6	5.2	6.1	7.3	9.3	15.0
Diuretics	6.3	7.5	9.4	11.8	15.2	18.3
Anti-hypertensives	4.7	5.1	6.1	6.6	7.0	6.6
Vasodilators and vasoconstrictors	5.4	4.9	5.0	5.4	5.9	2.4
Expectorants and cough suppressants	22.5	22.6	18.4	18.8	19.4	18.2
Asthma	—	—	—	—	—	12.5
Analgesics major[1]	1.1	0.9	0.8	0.7	0.6	4.3
Analgesics minor[2]	22.6	20.2	18.8	20.3	23.1	21.1
Sedatives and tranquillisers	16.1	18.1	20.2	22.7	24.3	24.8
Anti-depressants	5.3	6.3	7.7	8.3	9.1	7.8
Hypnotics (barbiturate)	17.9	15.8	13.0	10.7	8.2	17.0
Hypnotics (non-barbiturate)	5.3	7.2	8.7	9.9	11.7	
CNS stimulants	5.3	4.0	3.2	3.3	3.1	2.6
Appetite suppresants						0.3
Anti-convulsants	2.5	3.6	4.0	4.3	4.7	4.1
Anti-parkinsonism						1.5
Local anaesthetics and counter-irritants	5.1	3.4	3.0	2.9	2.7	2.7
Penicillins	17.3	17.9	17.7	19.9	19.8	20.0
Tetracyclines	13.4	15.5	13.0	12.1	11.1	9.7
Sulphonamides	3.4	2.6	1.8	1.4	1.2	0.9
Other antibiotics	4.0	3.5	3.6	4.7	5.2	3.1
Other anti-infectives	2.7	3.3	4.2	5.4	6.6	7.7
Oral contraceptives	0.8	0.9	1.0	1.1	4.1	6.4
Insulin[3]	1.6	1.8	2.1	2.2	2.4	2.6
Vitamin preparations	6.4	5.7	5.3	5.6	5.3	4.6
Eye preparations	4.7	4.3	4.1	4.4	4.7	5.8
Rheumatic preparations	6.8	7.3	8.9	10.1	12.0	15.2
Dressings and appliances	9.9	7.8	7.6	8.2	8.8	9.1

Notes
Due to a change of therapeutic classification, figures for 1977 are not strictly comparable with earlier years.

CNS = Central Nervous System.

[1] Prior to 1976, figures relate to addictive analgesics.
[2] Prior to 1976, figures relate to antipyretic analgesics.
[3] Including hypoglycaemic agents.

are preparations acting on the central nervous system, such as analgesics, antidepressants and tranquillisers (Figure 10). Trends over the period 1967-77 (Table 3) reflect two main factors: the ageing of the population and the introduction of innovations offering new treatment possibilities or displacing earlier therapies. Increases in the use of medicines like those acting on the cardiovascular system and those with anti-inflammatory activity reflect both these trends.

The average net ingredient cost of each prescription dispensed in 1978 was only £1.44 (at manufacturers' prices). Taking into account wholesalers' and pharmacists' margins and dispensing fees raises this figure to £2.16. Even so when seen in perspective it is clear that chemotherapy provides a highly economical means of treating ill health. Doctors are able to prescribe effective medicines for an ever widening range of disorders and this can generate important economic savings for example by facilitating a quicker return to work for those off sick and by easing the pressures on other branches of the National Health Service. Thus the rate of sickness benefit in November 1978 stood at almost £30 per week for a man with a wife and two children and avoiding just one week's stay in a large acute hospital in England would have saved £276 in 1978. The cost of medicines also appears in a favourable light against many items of consumer spending. The total cost of the NHS drug bill in 1978 (£723 million) was equivalent to a daily per capita expenditure of only 3.5 pence. This compares with average daily consumer spending of 88p on food, 37p on alcohol, 19p on smoking, 10p on entertainment and 36p on clothing.