THE ROCK CARLING FELLOWSHIP

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MEDICINES IN OUR TIME

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The Rock Carling Fellowship
was founded as an annual memorial
to the late Sir Ernest Rock Carling,
for many years a Governing Trustee
of the Nuffield Provincial Hospitals Trust
and Chairman of the Trust's Medical
Advisory Committee.

Each holder of the fellowship
will seek to review in a monograph
the state of knowledge and activity
in one of the fields in which Sir Ernest
had been particularly interested and which
is within the purposes of the Trust.
The arrangements provide that the
monograph will be introduced by a
public lecture to be given at a
recognized medical teaching centre
in the United Kingdom.

PREFACE AND ACKNOWLEDGEMENTS

It was a great honour to be elected to the Rock Carling Fellowship in memory of a remarkable man whose many interests besides surgery and administration included the use and abuse of drugs. My predecessors in the Fellowship have been distinguished medical scientists, and my pride at joining their company is tinctured with a justifiable diffidence, for I have no scientific pretensions. Nevertheless, I may have some qualifications to write on the subject allocated to me, for during my long tenure of the Chair of Therapeutics and Clinical Medicine in the University of Edinburgh I was much concerned with the clinical use of medicines and with the instruction of undergraduates and postgraduates in their administration: then after my retirement I was involved for a number of years (much to my own surprise) with measures to ensure as far as possible the safety of drugs in this country: and finally in the evening of my days I have for a short time joined the group board of an international pharmaceutical company. Possibly there are not many others who have had the opportunity to view the problems presented by modern medicines not only from the vales of academe, but also from the standpoint of a sort of honorary medical bureaucrat and from that of the pharmaceutical industrialist.

I have written this monograph not so much for the scholar or specialist in the subject as for the average educated man interested in it. It should be possible to write about it so that he will understand it without burdensome effort and the learned man will not despise it. To make for ease of reading the essay includes no tables of figures or graphs of statistics. Many volumes and papers have been published containing the facts and figures on which my monograph is based. Throughout the text references to these are given so that those desiring to delve in greater depth into any aspect of the subject will be enabled to do so.

Apart from mentioning them in the references (p. 95) it would take too long to express my gratitude to the numerous authorities

from whom I have derived valuable information, but I am particularly indebted to the following: D. Guthrie, *A History of Medicine;* M. H. Cooper, *Prices and Profits in the Pharmaceutical Industry;* F. H. Happold, *Medicine at Risk;* Wyndham Davies, *The Pharmaceutical Industry;* Paul Talalay, *Drugs in our Society;* H. F. Dowling, *Medicines for Man;* William Brecon, *The Drug Makers;* and several of Teeling-Smith's admirable publications from the Office of Health Economics. I am also grateful to the Editors of the *British Medical Journal,* the *Proceedings of the Royal Society of Medicine,* the *New Zealand Edition of Drugs,* and *Community Health* who have permitted me to repeat a few reflections about medicines which from time to time I have published in their columns.

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I

Historical aspects of therapy

Since the night of time men have employed plants and minerals in efforts to heal their diseases, to assuage their sufferings, or to cheer their mood. A Sumerian clay tablet and the famous Ebers papyrus of Thebes testify that polypharmacy was practised as long ago as 2000 BC (1); and the Bible bears witness to the use by Noah sometimes not wisely but too well of what is probably the oldest of all drugs (2). In the earliest times it was believed that a spiritual influence (which it is tempting to correlate with energy) pervaded the universe and that illness resulted from its evaporation from the body. The remedy consisted in its replacement by the animism of a drug. A later conception was somewhat similar, except that the spiritual matter of animism which evaporated from the body in illness was replaced by evil spirits which entered it. The latter could be cast out from the possessed person not only by apostolic and other healers but also by the demons contained in a drug which could also be used prophylactically to prevent the entrance of evil spirits into the body at all (3).

In the Oriental, Egyptian, and early Hellenic civilizations, medicine grew from the ribs of their respective priestcrafts and gods were substituted for animism and demons (4, 5). In fact Imhotep (6), the physician to the Egyptian king of his day, was later raised to the status of God of Medicine. Thus, treatment was mostly dispensed by magic, spells, invocations, and amulets (7*a*). This priestcraft medicine survived into the Middle Ages. Indeed witchcraft persisted into the eighteenth century and is not without a few devotees today. Perhaps the cynic may say that the use of placebos which play a not unimportant part in the practice of medicine nowadays is not far removed from the practice of magic long ago.

Contemporary with the golden age of Athenian civilization Hippocrates (approximately 450 BC) taught under his plane tree in Cos that a logical materialism and the application of natural

methods were more important in treatment than ancient superstitions and the forces of magic (8). The function of the physician was to study man as an end in itself, to leave aside the idea of any divine interference in his affairs and to treat suffering with compassion, taking the axiom of *non nocere* as a basis for his actions. Brushing aside mystery he based his treatment of patients upon direct observation of their symptoms. His views were later elegantly expressed in the first Latin textbook of medicine (*de Medicina*) by his aristocratic Roman admirer, Aulus Cornelius Celsus (9, 10). About three hundred years after Hippocrates, however, the door which he had opened to rational therapeutics was effectually shut again for centuries by Galen (AD 130–201), the personal physician to Marcus Aurelius (11). He believed disease to be due to a change in the humours of the body and classified medicaments into innumerable groups of herbal remedies which he claimed to have an effect on these humours. Such drugs were instruments only to be employed effectively by learned physicians. Galen was not only industrious and dogmatic but in addition must surely have been a remarkable man for there has been no one else in the long history of medicine whose authority brooded over its practice for so long and whose views were so strongly held that for hundreds of years it was heresy to challenge them. A tribute to his influence is that pharmaceutical products prepared from naturally occurring substances are still called galenicals.

In the Dark Ages following the decline and fall of the Roman Empire such progress as was made in medicine and pharmacy came from an Arabic culture (7*b*). The vast conquests by Islam in Persia, the near East, North Africa, Spain, and Sicily allowed the Arabs to dominate the trade routes from the East from which most of the ancient medicaments were imported, including the precious agents brought to Bethlehem by the Magi on the first Christmas Day. Students of medicine flocked to Baghdad where, according to Gibbon in *The Decline and Fall of the Roman Empire,* there were at one period as many as 860 physicians. The most distinguished of them were the Arab-trained Persians: Rhazes (865–935 AD) who first enunciated the idea that fever was not a disease in itself but Nature's protective reaction to it, and struck a relatively modern note by saying 'if you can help by foods then

do not prescribe medicaments, and if simples are effective then do not prescribe compound remedies'; and Avicenna (930–1037) (his name an abbreviation of Al Hussein Abou Ali Ben Abdallah Ebn Sina) who knew the Koran by heart at the age of 12 and became a physician at 16. Arabic medicine made little progress in medical theory but much in the practice of pharmaceutics, being responsible for elaborating the techniques of evaporation, distillation, and filtration. The Arabian culture which flourished for centuries achieved greatness by establishing libraries, hospitals, and schools of learning such as that of Salerno.

A school of alchemists (12) arose in Alexandria after the first century which did not confine its activities to attempting the transmutation of base metals into precious substances; for the ovens, flasks, retorts, and crucibles of the alchemist's kitchen became of importance in the preparation of medicines and ultimately in the science of chemistry, and Dioscorides developed some crude sensory and physical methods for testing botanicals. Though charlatans eventually brought alchemy into disrepute a number of distinguished scholars were bred in this school, the most remarkable of whom was Theophrastus Bombastus von Hohenheim (1493–1541) who styled himself Paracelsus. Though he often behaved like a mountebank and dabbled in astrology and occult arts, he was also a revolutionary reformer threatening the whole fabric of the medical establishment of his day, being the first important man daring to criticize the aphorisms of Galen, to pour scorn on his traditional pharmacopoeia and to insist that experiment was more important than tradition. His main thesis was that therapy must involve the internal use of drugs such as arsenic, iron, mercury, and sulphur, obtained through chemical processes. The revolution in treatment which Paracelsus initiated at the end of the fifteenth century was accelerated by the great voyages of Vasco da Gama and Columbus, making available a variety of new medicaments, including balsam of Peru, cinchona bark, coca, ipecacuanha, tobacco, and spices. The lure of the last was as great as gold, especially to preserve and flavour carcasses slaughtered in the autumn because of lack of winter feed.

Once the structure of the human body had been described with greater accuracy by Vesalius (1514–64) the stage was set for new

discoveries about the functions of its various organs (7c). The seventeenth century was notable for great advances in experimental physiology such as those made by William Harvey (13), in analytical chemistry by Robert Boyle (14), and in physics and mathematics by Galileo (15). Advances in treatment during the century were not, however, comparable. Indeed Voltaire who was born only fifty-two years after the death of Galileo and thirty-seven after the death of Harvey defined medical treatment as 'the art of pouring drugs of which one knew nothing into a patient of whom one knew less'. When he uttered this classical cynicism some two hundred years ago it was very nearly true, for till a short time previously thought had been largely deductive, still based on the authority of Aristotle and Galen.

When he was still very young Galileo became a lecturer at Pisa University and dropped a ten-pound weight and a pound weight simultaneously from the Leaning Tower to prove that the former would not fall to the ground ten times as fast as the latter. Aristotle, for whom we now tend to have a contempt not always based on familiarity, had maintained that it would, but neither he nor any of his successors throughout nearly 2,000 years had taken the trouble to find out whether what he said was true. The idea of doing so was a novelty and Galileo's disrespect for authority was considered abominable and, persecuted by the Inquisition, he had to take refuge in the free University of Padua.

The conflict of Galileo with the Inquisition was not merely the conflict between free thought and bigotry or between science and religion. It was the conflict between the spirit of induction and that of deduction. Those who believe in deduction as a way of knowledge have to find their premises somewhere: usually in a classic book; jurists from the Roman Law, Mohammedans from the Koran, Communists from the works of Karl Marx, Christian Scientists and osteopaths from those of Mrs Eddy and Dr Still respectively, and medical students from the vast textbooks which are written for them or from the dogmatic assertions of many of their instructors.

Galileo's predecessors had *known* how the world was created and what was man's chief end; the deepest mysteries of metaphysics

and the principles governing the behaviour of bodies were perfectly clear to them. Throughout the moral and material universe nothing was hidden, mysterious, or incapable of exposition in orderly syllogisms. As the rising sun scatters the multitude of stars, so Galileo's few proved truths about falling bodies and pendulums banished the scintillating firmament of medieval certainties and established doubt; and science during the succeeding years has owed its remarkable progress very largely to questioning all things, even those on which action has been based. Thus, Newton's law of gravitation had reigned so long and explained so much that it seemed scarcely creditable that it should ever stand in need of correction. Nevertheless, as the result of Einstein's discoveries, such correction at last proved necessary and doubtless this correction may in its turn have to be corrected. Indeed, through the web of scientific advance the woof of doubt has continually run so that there has usually been a reluctance, in Britain particularly, to deprive different views of a hearing. On the whole the opposite has been the case in other walks of life and in the politics of many countries where there has been the sacred book, the heresy hunt, the solemn excommunication by bell, book, and candle. Here one intellectual certainty has replaced another at the expense of a sufficient number of martyrs; and so long as education aims at inculcating dogmas, religious, political, ethical, and medical, fresh relays of martyrs will be necessary for every step in human progress. While it is unlikely that humanity will ever be able to dispense with its martyrs, it is difficult to avoid the suspicion that with a little more thought and a little less passionate belief their number might be substantially reduced.

By the beginning of the eighteenth century the battle between the followers of Galen and Paracelsus had ended in favour of the latter and chemical drugs were here to stay. In Cullen's famous work (16) medicines were arranged 'according to their agreeing in some general virtue' and their usage was recommended for certain patterns of recognizable symptoms: astringentia, tonica, stimulantia, sedantia, and so forth. During the century Lind (17) published his *Treatise of the Scurvy* (1753) but it was not till forty-two years later that the Lords of the Admiralty put his precepts

into practice and abolished scurvy from the Royal Navy, thereby causing British seamen to be known by the soubriquet of 'limeys'; and it was not until 1924 (one hundred and eighty years subsequent to Lind's *Treatise*) that the Cape Government took steps to eradicate the disease among workers in the South African gold-mines. In 1785 William Withering (18) published *An Account of the Foxglove and Some of its Medicinal Uses*. The active principle of the foxglove was extracted many years later: it took a long time, however, before digitalis was used effectively owing to its inaccurate standardization and the passion for prescribing it in inadequate doses in elegant, unstable, compound mixtures. Lastly, in 1796 Edward Jenner (19) performed the first vaccination against smallpox and published his discovery two years later. Unlike Lind's experience, vaccination, after a short period of fierce opposition from the medical profession, was enthusiastically and quickly acclaimed by the public, perhaps because an example was set by the privileged classes. Nevertheless, vaccination only became compulsory in 1856 by which time the incidence of smallpox was already declining.

In spite of these great discoveries, therapeutic advances in the eighteenth century could hardly compare with those in analytical chemistry, made under the influence of Robert Boyle, with the crystallization of the active principles of crude chemicals by Carl Scheele and the introduction of clinical observation as we understand it today by Boerhaave. Though Galenism had been overthrown no scientific therapeutics had replaced it: just a fierce allopathy of bleedings, sweatings, vomitings, and purgings. It was thought that 'no remedy was so powerful an antiphlogistic influence as mercury' (20). The natural revulsion to all this doubtless resulted in Hahnemann's (21) popularity, for homeopathy at least did no harm. It also contributed to the therapeutic nihilism of scientific physicians in the nineteenth and early twentieth centuries (22).

Anatomy, physiology, pathology, bacteriology, and diagnostic medicine have usually had to blaze the trail along which scientific therapeutics can eventually advance for it is impossible to treat properly unless it is known how the body is constructed and how it works in health, about the natural history of disease, the agents

of infection, and of what is the matter with the patient. Thus, at much the same time as Laënnec, the inventor of the stethoscope, was beginning to put diagnosis on a firmer foundation, some thirty million leeches a year were being used in treatment by his brother physicians in France, and up in Edinburgh the redoubtable Dr James Gregory (famous or perhaps notorious for the powder which bears his name) was complacently prescribing 20 grains of calomel (a fearsome dose) to one of the unfortunate lieges (23). When the great German pathologist Virchow, was revolutionizing pathology and altering our whole concept of disease, the pharmacopoeias then in use still included a mass of rubbish representing the relics of medieval folklore. For years after Robert Koch had made his monumental discovery of the tubercle bacillus, frock-coated and top-hatted physicians continued to clap respirators over the noses of their tuberculous patients, to exclude fresh air from their bedrooms as though it was a deadly poison, and to inject them with tuberculin and later with gold which did more harm than good. When Osler published his classical *Textbook of Medicine* about the turn of this century, therapeutic nihilism was still so rife that less than 10 per cent of the space in the first edition was devoted to treatment and much of that consisted of pious hopes and vague generalities: 'arsenic might prove useful'; 'the general health should receive attention'. Even the Edwardian physician who descended so impressively from his brougham to examine his patient, often with so much diagnostic skill, had to rely for treatment very largely on bottles of medicine elaborately prescribed, meticulously bottled, delicately flavoured, and exquisitely labelled but, as Oliver Wendell Holmes said, 'if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes' (26). It was all still faintly reminiscent of the witches in *Macbeth*, 'Fillet of a fenny snake, In a cauldron boil and bake'.

During the early part of the nineteenth century the philosophy of natural science became less empirical and biology, physiology, chemistry, and physics were integrated with medicine. Indeed, a number of physicians discarded practice in favour of the academic study of these disciplines. At this time, too, pharmacology became

a science seeking to identify the active substances in crude drugs and to establish their actions in the body. Atropine, bromine, caffeine, codeine, emetine, iodine, morphine, nicotine, physostigmine, pilocarpine, quinine, and strychnine were all isolated; and ether, nitrous oxide, chloral, and chloroform synthesized. In 1860 coal tar was used to synthesize salicylic acid, the first product resulting from research on dyes, and the synthesis of that remarkable drug, aspirin, followed in 1899. A few years later the German pharmaceutical industry produced barbitone (Veronal), the first of this well-known series of hypnotics. Thus, the modern tendency to regard the history of drug therapy prior to the chemotherapeutic and antibiotic era of this century as a prolongation of the Dark Ages is an exaggerated one (22*b*).

The greatest discovery of the century was that of Pasteur (25) (1825–95), a chemist not a physician, who established that infections were caused by germs and proved that it was possible to cause immunity against them by means of vaccines which he accomplished in respect of rabies and anthrax, while his assistants produced an antitoxin for diphtheria and another for tetanus. Before the end of the century effective vaccines had been developed for typhoid fever, cholera, and plague. Pasteur's work led Lister to introduce antiseptic surgery which in combination with anaesthesia made the century remarkable for its surgical progress. All these new drugs, including the bacteriological products inspired by Pasteur, required industrial methods for their production in bulk and could only be sold in pharmacies. Hence the rise in the importance of the pharmaceutical industry and some decline in the status of the independent apothecary though many of the great international pharmaceutical houses had their origin in modest pharmacies.

The German and Swiss industries (26) at the turn of the century developed more rapidly than those in Britain: they were not only more alert in recognizing the significance of synthetic chemicals but also received the close co-operation of academic medicine in research. In Britain, on the other hand, a rather highbrow distaste for anything connected with commerce was exhibited by academic research-workers which has not entirely dissipated even to this day. When Sir Henry Dale became

associated with Burroughs Wellcome with such admirable results there were many who said that he had sold his scientific soul for a mess of commercial potage. In consequence we relied heavily on Germany for pharmaceutical products till the First World War stimulated the rapid expansion of our own industries.

In the closing decades of the last century and the first decade of this one the great pharmacologist Paul Ehrlich (27), inspired by the work of Robert Koch (28) in the staining of histological specimens with dyes, explored the relationship between dyes and the living cells of the body and in the process produced Atoxyl, the first effective drug against trypanosomiasis, and Salvarsan (1910) against the spirochaete of syphilis. It is doubtful whether Ehrlich's work would have been possible without the close co-operation and great resources of Hoechst, the German chemical firm, as many hundreds of promising chemicals had to be investigated before final success was achieved.

Though, as has been said, it had been known for a long time that fresh fruit and vegetables could prevent scurvy, yet it was not till 1912 that Hopkins demonstrated scientifically that a natural diet contains tiny quantities of accessory food factors which are essential to health and which he called vitamins. Since then numbers of different vitamins have been recognized, synthesized in the laboratory, and their particular function in the body established. Their importance in human physiology and nutrition and their value in preventing deficiency disease is now well recognized.

One of the most exciting advances in the present century has been the isolation of hormones from the endocrine glands. Starting with the use of thyroid extract in thyroid deficiency at the end of the last century, it continued with the isolation of adrenaline, and Banting and Best's great discovery of insulin in 1921 (29). It is doubtful if there has ever been a medical discovery comparable in drama to the effect of the administration of those precious vials of insulin when they became available a few years later. Patients did recover from severe infections, even septicaemias, without the use of drugs, but those emaciated acute diabetics living on their impossibly high-fat, low-carbohydrate diets, surrounded by an aura of acetone, were invariably doomed

to rapid extinction. Further, though their subsequent management with diet and frequent injections was irksome and complicated, insulin itself had practically no toxic effects.

The same could be said about the next great advance in 1928, the treatment of megaloblastic anaemia by liver, the active principle of which was discovered twenty years later, for liver extract and vitamin B_{12} had practically no toxicity. Nevertheless, the saving of an elderly patient softly and silently vanishing away as the result of pernicious anaemia was less dramatic than the rescue of a child in diabetic coma.

In 1932 Domagk, the chief pharmacologist of the German chemical combine, I.G. Farben, discovered *Prontosil rubrum,* one of the innumerable dyes derived from coal tar which he had tested and whose remarkable activity against haemolytic streptococci turned out eventually to be due to the sulphanilamide group in its structure. The subsequent early sulphonamides, especially the famous sulphapyridine (M & B 693), though very effective were also fairly toxic.

An even more effective and much safer agent had been described in 1928, but it required the stimulus of war for it to be developed by Florey and Chain. With the introduction of penicillin the therapeutic explosion with which we are now familiar started in the 1940s, of which it is difficult to give shortly even a faint impression.

The discovery nearly thirty years ago that reserpine interferes with the retention of a number of amines mainly in the hypothalamus (that mysterious region in the brain where psyche and soma meet) and some twenty-five years ago that chlorpromazine is a potent inhibitor of many enzymatic processes, were the precursors of the new discoveries in psychopharmacology of the last ten years. These carry the promise of advancing our knowledge of the cause as well as the treatment of mental disorders. It is probable that drug treatment will eventually replace the crude therapeutic assaults on the brain of electro-convulsive therapy and surgery on the one hand and the prolonged, painstaking psychiatric analytical treatment on the other which hardly permits universality of application. It must be confessed, however, that our ignorance of the biochemical disturbances underlying psychiatric illness is still

profound; indeed it is uncertain to what extent such disturbances exist at all.

The first trials of chemotherapeutic agents on human tumours started as long ago as the trials of anti-tuberculous drugs, but whereas the latter quickly revolutionized the treatment of tuberculosis, the chemotherapy of malignant disease has so far only succeeded in sometimes delaying its fatal outcome, save in the case of methotrexate which seems in some cases to cure choriocarcinoma. Nevertheless, in the last fifteen years drugs have been introduced which significantly influence the survival time of patients suffering from leukaemia and tumours of lymphoid tissue. The benefits so far accruing from the vast research in this field are limited but may presage the dawn of the conquest of malignant disease.

The longing of diabetics for a hypoglycaemic drug which could be taken orally instead of having to be injected like insulin, was realized when the sulphonylureas and diguanides were introduced. Only some 30 per cent of diabetics are suitable for such treatment, but as diabetes is so common this represents a great blessing and a vast saving of inconvenience to many, especially to elderly diabetics with failing vision.

In the effort to keep up with the development of resistant strains of organisms many new antibiotics continue to be introduced. Their development against fungi is a significant advance in the treatment of superficial dermatomycoses. Lastly, a note of superficial optimism regarding the future of vaccines and of chemotherapy against viruses seems to be warranted.

In recent years major pharmacological advances have occurred in the treatment of hypertension, in diuretic therapy, and in the development of adrenergic blocking agents. Further, new drugs are banishing various tropical diseases from vast regions of the globe. It must be confessed that the latter are exacerbating the greatest problem facing mankind today, that of his terrifying multiplication. Thus, the oral contraceptives, introduced some twenty years ago, may represent the most important modern advance in pharmacology. Nature (as yet at any rate) does not seem to be exacting an excessive retribution. It is profoundly to be hoped she will not do so in the future.

The generation of physicians who qualified just after the First World War (now old men) have thus witnessed greater advances in treatment in their life-span than have occurred in all the previous aeons of time and there is no saying what the majesty and splendour of therapeutic progress will be in the quarter of the century which remains; we may even be able to prevent the common cold! Young physicians nowadays, armed with the therapeutic thunderbolts of Jove which the synthetic chemist has put into their often very ungodlike hands, must find it hard to imagine, just as elderly physicians find it hard to remember, what it was like to practice medicine when there was no insulin, vitamin B_{12}, sulphonamides, antibiotics, hypotensives, anticoagulants, specifics for tropical diseases, potent diuretics, anticonvulsants, and hormones.

2

The discovery and innovation of medicines

It is popularly supposed that most great modern therapeutic advances have originated from the sheer intellectualism of the discoverer, planning his research with a certain objective in view (30). Sir Henry Dale's great original exposition on histamine and acetylcholine and Sir Rudolph Peters's introduction of dimercaprol (British anti-lewisite) were indeed elegant examples of this planned but uncommon intellectual approach to discovery.

Pharmacological advances originally stemmed from the discovery and isolation of biodynamic substances in folklore medicine, substances culled from the hedgerows, so to speak: the poppy, the cinchona bark, rauwolfia, the coca leaf, the rye fungus, and so forth. Their active principles were eventually isolated by chemical methods to give morphine, quinine, reserpine, cocaine, and ergotoxine. Then, through the development of pharmacologic methodology and ingenious chemical juggling with the original molecule, a new substance might be found showing interesting and often unexpected properties and for which the pharmacologist looked for a disease to fit it to, just as a locksmith, having made a key, might seek a lock for it to open.

Thus, attempts to simplify the complex molecule of quinine which had eventually been isolated as the active principle of the cinchona bark led to the production of other effective antiplasmodial compounds. During the study of their pharmacological properties Bovet observed unexpectedly that they had an antagonistic action to histamine and this observation resulted in the introduction of the anti-histamine drugs. The original antihistamines were noted to have a markedly soporific effect and to prevent travel sickness: observations which led in turn to the

phenothiazine tranquillizers and the modern anti-emetics. Thus, quinine, the synthetic anti-malarials, anti-histamines, phenothiazine tranquillizers, and anti-emetics all stem from the ancient, traditional seventeenth-century remedy: Jesuits' bark.

There are many other examples of this pharmacological house that Jack built such as the rye fungus (*Claviceps purpurea*), ergot and its alkaloids, methysergide, and lysergic acid (LSD)—that most controversial of hallucigenic drugs which may, however, have loosened a chink in the magic casement opening on the mechanism of mental processes or rather on the biochemistry of mental disease.

Though, as has been said, anatomy, physiology, pathology, microbiology, and diagnostic medicine have usually had to blaze the trail along which scientific therapeutics could advance, there are a number of examples of effective therapy being fortuitously stumbled upon long before the cause of a disease or the mechanism of its symptomatology have been elucidated. Marcus Cumanus, for example, knew nothing about the *Treponema pallidum* when he advocated mercury for the treatment of syphilis in 1495. The Jesuits were not conversant with the *Plasmodium vivax* when they introduced their bark in 1630. Lastly, in 1894 when Dr William H. Thomson in New York described the dramatic relief of a number of patients suffering from 'periodic neuralgia' by the use of ergot, he was unaware of the abnormal cerebral circulatory function of migrainous patients. Indeed, he resembled the description of Mr Tupman out shooting in *The Pickwick Papers* who, after surmounting the difficulty of discharging his piece at all, would shut his eyes firmly when any birds got up and fire into the air; yet on one occasion after performing this feat, Mr Tupman on opening his eyes beheld a plump partridge in the act of falling to the ground.

It is indeed a sobering reflection that many important therapeutic developments have been due to pure serendipity: fortuitous observations acting on the prepared mind such as the famous discovery of penicillin, and even from entirely fallacious hypothesis. For example, Sir Charles Locock in 1857 advocated bromide

for the prevention of epilepsy, not for its depressant action on the motor cortex which was subsequently demonstrated, but because it was a well-known anaphrodisiac and masturbation was then thought to be an important aetiological factor in epilepsy; a threat which caused grave concern to generations of Victorian schoolboys. Again, the treatment of pernicious anaemia by liver was promoted because Minot and Murphy found that dogs rendered anaemic by repeated bleedings recovered more quickly from their consequent iron deficiency anaemia on a diet of liver than on any other food. This recovery was due to the very high iron content of liver and had nothing whatever to do with its ability to convert the megaloblastic bone marrow of Addisonian anaemia into a normoblastic one. Lastly, the recognition of the beneficial effects of ergotamine in migraine rested on a similar mistaken reasoning: Dale's classical work in 1906 demonstrated that preparations of ergot in large doses diminish the responses of smooth muscle to adrenergic nerve stimulation and to epinephrine; because of this ergotamine was tried as a therapeutic agent in migraine in 1928 as it was believed that the headache resulted from spasm of the cranial arteries following excessive sympathetic stimulation and that ergotamine caused their relaxation. Of course, the exact opposite is the case and the effects of ergotamine in the small doses used clinically do not produce the adrenergic paralysis caused by large doses but rather vasospasm to which ergotamine owes its beneficial effects.

Many valuable new remedies have developed from the observation, again acting on prepared minds, of the unexpected side-effects of drugs: thus, polyuria noted by an observant nurse during the treatment of a syphilitic by mercury led to the introduction of mersalyl; the association of an alkaline urine with a metabolic acidosis during sulphonamide therapy started the research which culminated in the thiazide diuretics; hypoglycaemia, observed after giving sulphonamides to undernourished patients suffering from typhoid fever in occupied France during the last war, stimulated the development of the hypoglycaemic sulphonylureas; the phenothiazine tranquillizers stemmed, as we have seen, from the rather annoying drowsiness experienced by patients taking the

original anti-histamines; and the anti-depressants developed from the euphoria noted in some tuberculous patients undergoing treatment with isoniazid. Doubtless further developments in treatment will so eventuate in the future.

In the last fifty years some great new therapeutic agents have been discovered by academic workers in university departments or in national research institutes. These include penicillin, insulin, the liver treatment of megaloblastic anaemia, dimercaprol (BAL), the oral hypoglycaemic sulphonylureas, streptomycin, griseofulvin, cephalosporin, and interferon. Most of them have required the collaboration of research workers in pharmaceutical firms and the vast resources of industry for their development. Apart from such notable exceptions, however, the great majority of new medicines introduced this century have not only been developed but also discovered by scientists working in the laboratories of an industry devoted to the profit motive, but in which there is nevertheless no sharp dividing line between 'applied' and so-called 'pure' research. A measure of the innovative success of the industry may be gauged from the fact that of the 150 medicines most commonly prescribed in Britain today only 22 were known in 1946.

Some of these advances in chemotherapy result from an enlightened screening process for which industry is particularly well suited in policy and facilities (31). Thus, thousands of compounds, synthesized because of their known value in certain conditions, are screened to ascertain if they might be of value for other purposes. For example, the hypotensive drug, guanethidine, was discovered by screening compounds of value in trypanosomal infections; probenecid, synthesized to delay the excretion of penicillin, is now mostly used to increase the excretion of uric acid in the treatment of gout; and Diamox, introduced as a diuretic, is now never used for this purpose but is valuable in the treatment of glaucoma.

Perhaps, however, the main preoccupation in the laboratories of most firms and the one which yields the major portion of success consists in making modifications of the chemical molecular

structure of preparations known to have a certain pharmacological action in the hope that the modification may produce a more effective or safer drug than the original one, or in rare instances an important new therapeutic agent. These screening processes and this molecular roulette do not exclude basic theoretical research directed to the understanding of physiological processes and problems of unconquered disease. The investigation of the relationships between pharmacological action and chemical structure at molecular and cellular level is most apt to produce major advances like that of the discovery of the penicillin nucleus on to which other chemicals could be grafted.

The method of minimal molecular manipulation undertaken to circumvent patents has come in for much justifiable criticism and has resulted in a very large number of preparations differing only very slightly from each other and known by a bewildering number of names (32). These have certainly proved confusing and embarrassing to the medical profession. On the other hand it is undesirable to denigrate unduly these drugs, often referred to disparagingly as 'Me Too' drugs, for just as the 1973 motor-car has been gradually developed over the years, usually by very slight changes on earlier models, so the modern pharmaceutical product may eventually constitute a very considerable improvement on the original. Which of us, for example, would use sulphanilamide or sulphapyridine in preference to the modern sulphonamides and who, except for replacement purposes, would prescribe the original cortisone rather than more recently introduced corticosteroids? Lastly, one of the greatest advances in the antibiotic field in the last twenty years (the isolation of the penicillin nucleus) might be described as a 'mere' molecular manipulation. It is difficult for the medicinal chemist to know when he undertakes the synthesis of a new molecule whether he will be accused of having indulged in a trivial effort or whether he will be praised for having achieved a major discovery. In a free society people must not be discouraged from using their brains though their excessively courageous ebullitions may have to be controlled.

3

Benefits of modern medicines

In the 1940s and early 1950s it almost seemed that the therapeutic millenium was approaching and the advent of each new medicine was hailed with wonder and acclamation. The press and radio were filled with accounts of amazing 'breakthroughs' in therapy and 'wonder' drugs constituting the philosopher's stone in treatment. In recent years the pendulum has indeed swung violently in the opposite direction and drugs, far from being considered beneficial agents, are often regarded as a threat to the integrity of the human body or even to the structure of society. The word 'drug' like that of 'love' has developed undertones as well as overtones and a pejorative connotation recalling 'drug addict', 'dangerous drug', 'under the influence of drink or drugs', and so forth. Indeed henceforth, it would be more appropriate in this monograph to substitute 'medicine' for 'drug' when using the word to indicate a substance employed in the treatment or prevention of disease.

Both the extreme attitudes to medicines mentioned above are, of course, exaggerated and harmful, but it is perhaps appropriate in the rather hysterical anti-drug atmosphere which presently exists to recall the vast benefits which the use of modern medicines has conferred on society. In the next chapter the adverse effects which are inseparable from the employment of all effective medicines and the dangers accompanying their unwise use will also, of course, be referred to.

The whole natural history of disease and mortality have been profoundly altered by modern medicines which have conferred the greatest benefits on us. Since 1930 the mortality from gastro-intestinal infections, the chief cause of deaths in infancy, has fallen by over 80 per cent, and the Office of Health Economics in its pamphlet estimates that 380,000 people now alive in the UK would have died in childhood had the death-rates of the early 1930s not

improved (33). In the same period deaths from pulmonary infections have fallen by some 70 per cent while the mortality from tuberculosis (34), meningococcal infections, mastoiditis, and venereal disease (35) all show similar or greater declines. It is true that in recent years there has been a disturbing increase in notifications of venereal disease due to our permissive society, but this has not so far affected the fall in the death-rate from this cause. Diphtheria, from which as late as 1940 there were annually some 4,000 fatal cases in England and Wales alone, has practically disappeared, and the same can be said for puerperal sepsis which caused hundreds of deaths each year till the 1930s. Typhoid, plague, cholera, yellow fever, tetanus, rabies, smallpox, measles, and poliomyelitis can all be prevented by prophylactic vaccinations. Many tropical diseases like malaria have been controlled. The lives of patients suffering from diabetes and megaloblastic anaemia can be preserved. Thus, since the 1920s some 2,000 fewer diabetics (36) die every year and the mortality from pernicious anaemia has been reduced by 80 per cent since the 1930s. Great relief and prolongation of life have been given to sufferers from hypertension, rheumatoid arthritis, asthma, and many nervous and mental disorders. The list is far from comprehensive and makes inadequate mention of the relief from suffering which the purely symptomatic use of modern medicines confers or of the saving to the national economy consequent on the diminished morbidity which results from their use, such as less time lost from work and fewer and shorter admissions to hospital. For example, it has been estimated with fair accuracy that the saving to our economy each year from the use of modern anti-tuberculous medicines alone is about £55 million or about a quarter of the total medicines bill under our National Health Service (37).

It is somewhat paradoxical after making this statement to note that more people attend their doctors, visit out-patient departments, and are admitted to hospital than ever before and the costs of the NHS continue to spiral. This is not a reflection on the benefits conferred on society by modern medicines but simply draws attention to what has been called the clinical iceberg which existed formerly and still exists to some extent in which only the tip represented those who received medical attention while the

submerged nine-tenths represented those cases of untreated and probably undetected illness. It makes nonsense of Lord Beveridge's expectation, shared by Aneurin Bevan, that the initial costs of the NHS would gradually diminish as the health of the population improved as the result of it. People have quite rightly grown to expect treatment for conditions a short time ago often stoically endured without thought of medical intervention. Propaganda which encourages the public on the grounds of public health to visit their doctors, to be X-rayed, and to have regular medical check-ups also increases the apparently insatiable appetite for medical care. The resulting paradox is that while the population has obviously become healthier it is now demanding and receiving much more medical treatment.

Of course, the all-round improvement in social conditions has contributed as well as medicines to the fact that since 1930 the average expectation of life of men and women in this country and the United States has increased by over ten years. The steady improvement in hygiene, housing, nutrition, and standards of public health has been responsible for the slow but significant decline in mortality rates which have occurred since vital statistics became available last century. Nevertheless, one has only to look at the curve of these gradual declines in mortality and note the precipitous fall in them which results in so many diseases when specifics are discovered for their treatment to realize that the use of medicines, including bacteriological products, has been an even more potent factor during the last thirty years in reducing mortality rates than has the improvement of social conditions.

As the result of all this the pattern of disease which we see nowadays has changed out of recognition. Most hospitals for tuberculosis and many wards for infectious diseases have been closed or given over to the care of bronchitics or old people. Young people between the ages of 15 and 30 seldom die from disease nowadays, the chief cause of death among them being accident, mostly on the roads, the second suicide, and the third, a long way behind, the comparatively rare group of diseases, the acute reticuloses, including acute leukaemia. The atmosphere and length of stay in our mental hospitals has improved out of recognition owing to the use of modern psychotrophic medicines.

Most of the recent great surgical advances have only proved possible as the result of advances in chemotherapy, including modern anaesthetics. Lastly, our general hospitals are filled to a large extent with patients suffering from the ordinary processes of ageing, such as atherosclerotic cardiac, and cerebrovascular disease which now constitute the chief causes of death.

4

Adverse reactions to medicines

Adverse reactions to medicines (38, 39) are part of the price we pay for more effective remedies. Just as the old horse and buggy, though very slow caused few fatal accidents, whereas the modern motor-car is a lethal instrument, so the old-fashioned bottle of medicine, though relatively ineffective was also comparatively innocuous, whereas the modern medicine like atomic energy is powerful for evil as well as for good. Ill-health due to medicines (iatrogenesis as it is called, or more optimistically if a little ironically, illness due to medical progress) has become a new dimension in the aetiology of disease. Perhaps some 10 per cent of our patients suffer to a greater or less extent from our efforts to treat them. Our powers over Nature in this as in other respects have advanced so far that Nature seems to have become retaliatory and to be exacting a massive retribution.

There is no such thing as a completely safe and effective medicine: some are safer than others; especially those given to replace something which the body lacks, such as vitamin C in scurvy or thyroxine in thyroid deficiency; when administered in correct doses for replacement purposes such medicines seldom cause adverse effects. Most medicines, however, are given for their pharmacological effects, to modify or repress some biological process. Without this ability they will be useless in treatment but if they have it they are bound to cause adverse effects from time to time. Those who say that nothing but the complete safety of medicines will suffice demand the impossible. The public that are anxious for progress must be prepared for some risk. For example, they have always been ready to accept the not inconsiderable risks of surgery to which some modern medicines are equivalent in efficacy: they shudder at a death-rate of, say, one in 40,000 patients as the result of taking a valuable remedy (and which surgeon incidentally would not be enchanted with such statistics for the most minor operation?) but are more complacent

about the much greater hazards of cigarette smoking, alcoholism, or death on the roads.

The term iatrogenic disease has, of course, a far wider connotation than ill-health due to taking medicines for it means ill-health due to treatment in general and includes inexpert or ill-advised surgery, radiotherapy, and faulty doctor–patient relationships in which patients have all too frequently been traumatized by thoughtless remarks dropped within their hearing or said directly to them. Every word, expression, and inflection of speech on the part of a doctor at a medical consultation is charged with portent for the patient and afterwards often endlessly pondered over and sifted for a possible sinister meaning. The iatrogenic psychological illness created by ill-judged, insensitive, or thoughtless remarks by physicians may disable a patient far more than the less serious forms of adverse reactions to medicines or the possibly trivial organic disease for which he has sought advice. The sins of omission, too, on the part of doctors may equal those of commission: failure of communication so often results in the frequently heard pathetic remarks by patients and their relatives such as 'they never tell you anything', or 'we didn't like to ask'.

We are a medicine-swallowing people and it is in the nature of medicines to put at risk those who have recourse to their healing powers. The next time a calamity like the thalidomide disaster strikes us (and there is no absolute guarantee of its prevention though it would be recognized more expeditiously) there may not be a rich and vulnerable firm like the Distillers' Company to act as a convenient scapegoat to ease the nation's conscience. Nevertheless, with propriety, wisdom, and skill in their prescription and use, and with sensible control regulations the dangers of modern medicines can be minimized, and a proper understanding of these dangers is the first step to their intelligent prevention. The mechanism of development of adverse reactions is often complex and ill-understood but a provisional classification may prove to be of some help (40).

1. *Overdose*

Overdosage is the simplest and most obvious cause such as sickness from digitalis, fainting from hypotensives, or haemorrhage from

anti-coagulants. Under this heading too must be included accidental poisoning and self-poisoning. The latter is usually a preferably term to suicide, as the subconscious motive of the majority of people who poison themselves is to create a crisis providing an escape from intolerable personal problems rather than actually to kill themselves, though they often succeed in doing so.

In recent years self-poisoning (41) has assumed epidemiological proportions and now constitutes the second most common cause for emergency admission to our general hospitals. There are certain countries where deaths from suicide are common (West Berlin: 35 per 100,000), some with a moderate rate (UK: 8 per 100,000), and others with a very low rate (Malta: 1·5 per 100,000) and this pattern is roughly maintained when the inhabitants emigrate to other countries. It is perhaps significant that the four countries with the lowest rate of deaths from suicide should be devoutly Catholic (Italy, Spain, Eire, and Malta). On the other hand deaths from this cause in those countries tend to be under-reported in order to allow for appropriate burial rites. The epidemic seems also to be more common in welfare states than in countries where the primary concern of the population is the difficulty of securing sufficient food, clothing, and shelter to keep alive. It corresponds with the increased use of barbiturates, tranquillizers, and mild analgesics. Such agents offer a more comfortable means of self-destruction than hanging, throat-cutting, drowning, or drinking lysol. Further, it is easier in some domestic crisis to draw attention to oneself by taking a handful of pills from the family medicine cupboard than to develop an attack of the vapours or hysterics which was a more common reaction to an intolerable situation in days gone by.

The easy accessibility and ready availability of medicines is of great importance in the accidental poisoning of little children as well as the impulsive acts of self-poisoning which have been referred to. A careful and now famous investigation of some 500 households in the north of England industrial town of Hartlepool disclosed in their medicine cupboards 43,000 unused tablets and capsules, 16,000 of which had been prescribed for their action on the central nervous system. Based on the number of households

and the 100,000 population of Hartlepool it was calculated that approximately 2,500,000 tablets or capsules might be so available in the whole town, and that if Hartlepool is at all typical of Britain (and there is no reason to believe that it is a very unusual place) this would represent one and a quarter billion unused items in the UK at a basic cost to the NHS of approximately £6,500,000.

Defective renal or hepatic function may result in relative overdosage. Thus, dangerous concentrations of streptomycin in the blood may occur from conventional doses given to people with inadequate renal function and babies are notoriously intolerant to certain medicines like opiates owing to the immaturity of the hepatic enzyme systems which metabolize them. Indeed recent studies in pharmacogenetics show that the speed of metabolism of many medicines is related to genetically determined hepatic enzyme activity and constitutes one of the growing points in our understanding of ill-health due to medicines, explaining some adverse reactions previously vaguely ascribed to intolerance or idiosyncracy. Thus, a medicine prescribed in the same dose may be ineffective to one patient and toxic to another.

2. *Interactions between medicines* (42)

The incompatibility of drugs to each other in the old-fashioned bottle of medicine which formerly constituted a bugbear to prescribers is not now important. It is possible, however, as we shall see, that insufficient concern is shown regarding the effect on the metabolism of other medicines of agents like phenobarbitone so often included in compound preparations. The syringe and infusion bottle may sometimes be the site of undesirable interactions if medicines are mixed in them, since one of the added agents may be precipitated and inactivated by another.

A more serious problem, however, is the frightening number of medicines which patients often take or are given nowadays simultaneously, the pharmacokinetic reactions between which are immensely complex and ill-understood; often not comprehended at all by their blithe prescribers. It is common to encounter bewildered old people taking three, four, or even five different tablets containing potent remedies in the course of the day, and getting them all muddled up in the process. Nor does this only

occur in practice, for such polypharmacy is just as common in hospital. Some years ago, for instance, an investigation was undertaken in the Johns Hopkins Hospital at Baltimore, where the standard of therapeutics is certainly not below the average, into the then new penicillin, methicillin: it was found as a side-effect to the investigation that of the in-patients in the trial the average number of other medicines they had had besides methicillin during their stay in hospital (including laxatives and hypnotics) was 14; the least any had received was 6; and one patient had had 32!

Not only may a patient have a number of medicines prescribed simultaneously for him by his doctor, but at the same time he may purchase for himself and unknown to his doctor a number of simple remedies which do not require a prescription such as mild analgesics, laxatives, cough mixtures, and preparations for the relief of colds. Notwithstanding their seemingly innocuous nature these may interact with more potent agents prescribed contemporaneously to cause significant changes in the absorption, distribution, metabolism, and excretion of the latter.

The speed and completeness with which medicines are absorbed from the gut or from an injection depend on factors which can be modified by other agents given simultaneously. Such factors include intestinal motility, blood supply, viscosity, surface tension, pH, and solubility. Other medicines affecting these factors readily spring to mind.

Following absorption many medicines are transported in the body bound to plasma proteins. Their pharmacological activity, however, depends on the concentration of the factor free to diffuse and unbound to the plasma albumin. A toxic effect may, therefore, result if the level of the unbound fraction is increased by another medicine competing for the same site on the plasma albumin, and particularly if it has a greater affinity for it. Thus, the concentration of active warfarin (the anti-coagulant) can be greatly increased by a slight reduction in its binding and there are several commonly used acidic medicines which are extensively bound to the same site on the serum albumin. It is, therefore, obvious that unless great propriety is exercised in the selection of medicines prescribed with it haemorrhage may result from warfarin administration.

Most medicines are lipid soluble which facilitates their absorption from the alimentary tract but it would also cause them to be reabsorbed again by the renal tubules. Thus were they not metabolized in the body to excretable forms they would be doomed like the Flying Dutchman to rove the seas of life almost indefinitely. The most important metabolic reaction is the oxidation of medicines to excretable forms by hepatic microsomal enzymes. As we have seen the activity of this enzyme system can vary genetically but it can also be stimulated or depressed by medicines. Many of these use the same metabolic pathways and should one medicine either inhibit or stimulate that particular enzyme then all the others metabolized by that system will be similarly affected.

Phenobarbitone is the classic medicine with the ability to stimulate the activity of microsomal enzymes and so to induce the metabolic destruction of a large number of medicines in common use and in consequence to reduce their pharmacological effects. As some medicines such as the barbiturates can stimulate their own metabolizing enzymes this may contribute to the phenomenon of tolerance. On the other hand, if the metabolism and hence the elimination of a medicine is reduced by the contemporaneous administration of a second one, then the effects, both therapeutic and toxic, of the first will be enhanced and this happens not infrequently. Perhaps the most striking examples are the toxic effects produced when disulfiram (Antabuse) is given with alcohol, while the results of giving sympathomimetic amines and foods containing tyramine at the same time as mono-amine-oxidase inhibitors are notorious.

The action of a medicine is ultimately due to its becoming adsorbed on to a receptor in or on a cell. Many medicines compete with each other for the same receptor site and their relative concentrations and affinities will determine which has the dominant effect. Adverse effects may result from this competition: thus the action of pyridostigmine in myasthenia gravis is abolished should streptomycin be given simultaneously, and amphetamines reverse the adrenergic neurone blockade of guanethidin and methyldopa.

Lastly, medicines may interact during renal excretion by inhibiting or altering each other's tubular transport, glomerular

filtration, or urinary pH. Adverse as well as benign actions may result.

From this brief review of the interactions which may occur between medicines it is plain that with the increasing potency of modern therapeutic agents an ever-increasing risk attends their simultaneous use and we should be cautious of prescribing more than one medicine at a time unless we know what we are about. On the other hand, while recognizing that such interactions are sometimes the cause of toxic reactions, it is important to avoid the almost hysterical attitude adopted about them by some pharmacologists. As Prescott (43) has said, enormous lists of real or imaginary interactions have been published with warnings of dire consequences if virtually any two drugs are given at the same time. For all that has been written on the subject the degree of clinical importance which we should attach to drug interactions is not well established. Potentially lethal interactions such as the potentiation of anti-coagulants, oral hypoglycaemic agents, and cytotoxic drugs are of the utmost importance but it is probable that many other interactions are mainly of academic interest.

3. *Side-effects due to widespread action*

Some medicines like penicillin are remarkably selective in their action. Others like corticosteroids, besides the desired action for which they may be prescribed, have additional widespread unwanted effects. Thus, atropine given to allay spasm or reduce secretion may cause blurring of vision or glaucoma; and morphine given to reduce pain may also produce vomiting, constipation, and respiratory depression.

4. *Secondary effects*

These are the possible consequences of a medicine's action and not the primary effect of its administration. Thus, the destruction of white cells by medicines used in the treatment of leukaemia may release such quantities of nucleo-protein into the blood as to cause uric acid urinary calculi or an attack of gout. Tetracyclines may sweep and garnish the bacterial population from a patient's intestines leaving an organismal vacuum in which fungi flourish,

resulting in the orogenital syndrome. Anti-malarials may so increase the survival rate of a population relative to its food supply that their secondary effect may be starvation. Lastly, drug addiction is an indirect secondary consequence of drug action.

5. *Hypersensitivity reactions*

These are antigen-antibody reactions conditioned by previous exposure and sensitization to a medicine. If the medicine is a protein it can itself act as an antigen; otherwise, combined with a plasma protein it forms an antigenic combination. Such reactions, due to the liberation of histamine-like substances, may constitute some of the most alarming toxic effects such as the anaphylactic shocks to antitoxins or penicillin. Hypersensitivity reactions also include cutaneous eruptions, photosensitivity, hepatic necrosis, arteritis, bronchospasm, and blood dyscrasias. Aplastic anaemia is the most serious of the latter as it is so often irreversible.

Before 1930, drug therapy did not greatly alter the natural history of disease so that in eliciting a medical history the medicines a patient had been taking recently was not a matter of great concern. The therapeutic revolution of the last forty years has given us remedies which not only powerfully affect the course of many diseases but may produce signs and symptoms closely resembling naturally occurring disorders, thereby obscuring the correct diagnosis. Further, it is most undesirable to anaesthetize or operate on patients being treated by certain medicines like corticosteroids without taking precautions, and the danger of giving unsuitable medicines to patients already taking, say, monoamine oxidase inhibitors, has been mentioned. Thus, it is of paramount importance to ascertain what medicines a patient has been having recently. Yet the tradition of ignoring this essential part of history-taking dies hard and inquiries about recent therapy may be deferred till after numerous laborious, expensive, and perhaps disagreeable investigations have been undertaken to elucidate obscure symptoms in reality due to iatrogenesis.

The neglect to record previous treatment may sometimes be due to the difficulty of ascertaining what medicines the patient has actually taken. He may have purchased 'over the counter' medicines unknown to his doctor. Then patients are nowadays often looked after by more than one doctor and communications between partners in practice, from practitioners to consultants and consultants to practitioners do not always include this vital piece of therapeutic information. The patients themselves may not know the names of the medicines they have consumed and the container, often produced by them in an effort to be helpful, has till recently seldom carried more informative inscriptions than 'The Tablets' or 'The Mixture'. Fortunately the name of the contents must now appear on the label of the container unless otherwise specified by the prescribing doctor. This long-overdue pharmaceutical reform is to be welcomed and will conduce to the safety of medicines.

5

Doctors and medicines

At the end of the century Robert Louis Stevenson wrote, 'Where are men and classes of men that stand above the common herd: the soldier, the sailor and the shepherd not unfrequently; the artist rarely; rarelier still the clergyman; the physician almost as a rule. He is the flower (such as it is) of our civilization.' The doctor was then typified by Frith's famous Victorian picture of him as a bearded man in the cottar's home pondering over the fevered child on a makeshift bed with the two distraught parents in the background and the inevitable bottle of physic on the table. We must not denigrate him: there were very few other educated gentlemen (to employ an old-fashioned expression now largely reserved for use over public conveniences) who then went into cottars' homes, and they gave comforting reassurance and wise advice; and the medicine, if probably ineffective, was also usually innocuous. It is possible that the modern doctor after diagnosing pyrexia of unknown origin would hurriedly prescribe a sulphonamide; if on hearing over the telephone that the fever none the less continued, would order a broad spectrum antibiotic from the pharmacist to be called for; and should this also prove ineffective might find himself in some bewilderment as to whether the fever was due to the continuing infection or to the treatment given.

Nevertheless it would be pleasant to think, and it might still be the case, that RLS's encomium continues to apply, for by and large there are few other big groups of men and women in the world who are on the average as intelligent, well educated, industrious, compassionate, and altruistic as doctors. Further, the doctors of the future, the present medical students, seem to be superior to their predecessors. Up to thirty to forty years ago anyone, provided they were financially able to do so and were not half-witted, could become enrolled as a student at one of our medical schools, and with persistence would almost certainly qualify in the fullness of time. Those concerned with the assessment of

medical students today are unanimous that their average intellectual standards have improved due to their far more careful and stringent selection from the wider spectrum of society, resulting from the disappearance of the financial barrier. In some schools, for instance, 150 students may ultimately be selected from over 2,000 applicants. No wonder it is now most exceptional to encounter among them the inept and ignorant 'chronics' who were far from uncommon in the old days and whose bloomers at examinations provided the stories and banter which enlivened the luncheons of examiners.

The craft of medicine in the past with its middle-class origins was largely hereditary. Its present broader base can only be beneficial to society for the doctor should be classless. A hundred years ago Lady Chettham, in George Eliot's great novel, *Middlemarch,* expressed the views then generally held by her class: 'for my part I like a medical man more on a footing with the servants'. A hundred years ago the doctor when he dispensed advice to the lower orders in hospital often did so with condescension. His intellectual and technical standards are now probably greater but it would be a pity if he were to lose the human qualities and sense of vocation of his predecessors.

As regards the use of modern medicines the medical profession is not blameless. We have seen that effective medicines can never be entirely safe, yet their dangers could be minimized were they always prescribed and used with skill, wisdom, and propriety, for a considerable proportion of their adverse effects result from their excessive, irresponsible, or unwise prescription. Our country is not exceptional in regard to the over prescription of medicines: indeed, in the western world the only two countries where medicines are not used more extensively are Denmark and certainly Spain. It is surprising that in a Communist country like Hungary over twice as many prescriptions are issued per head of population per year than in the UK.

Great excess elsewhere, however, does not justify our excess and we must confess that there is much over-prescribing in Britain due to several causes. There is the insatiable demand for

medicines by the public for, as Osler said, the desire to take medicine is the chief thing differentiating man from the lower animals, and as a profession we are too apt to pander to the public's 'wants' rather than to what we think are their 'needs'. Then there are too few doctors for our increasing population (44) so that most are busy and some overworked. While it takes a long time to elicit a careful clinical history, to conduct a full physical examination, and to give wise advice, it only takes a moment to scribble a prescription for a placebo which often does please and satisfies the patient. Thus in our over-crowded out-patient departments in hospital and surgeries in general practice we have nearly all over-prescribed at some time in order to get luncheon or supper, and once started the habit is apt to grow. Doubtless the prescribing of placebos is occasionally justifiable when expectant treatment is indicated or just to give hope, but the better the doctor the fewer placebos he prescribes for a good doctor is a placebo in himself, deploying his personality as an instrument of therapy. If they *are* prescribed, placebos should be cheap, innocuous, and with a minimal pharmacological action. In the old days our 'tonics' fulfilled these criteria, the modern tranquillizers do not. Lastly there is the insistent, skilful, and sometimes informative promotion of medicines by the pharmaceutical industry, but which, in the past at any rate, was often subject to justifiable criticism. This problem will be discussed later (p. 38).

Prescribing is also often injudicious as the result of inadequate information and ignorance about medicines: their indications and contra-indications, their absorption, metabolism, and excretion, their widespread actions, and their complicated interactions with each other which are incompletely understood and sometimes not appreciated at all by their prescribers. This lack of knowledge is due to a significant extent to inadequate undergraduate and postgraduate instruction on the subject. While this was of less consequence in the old days of galenical medicines which did not greatly alter the natural history of disease, it is now of paramount importance that doctors should be more familiar with the formidable modern tools of their trade. Yet, till recently in most

medical schools throughout the world (though not in the Scottish ones), pharmacology was taught entirely as a pre-clinical science, usually by pharmacologists who had not seen a patient since they were house physicians and occasionally by scientists not themselves medically qualified. Such academic pharmacology is a valuable scientific discipline, necessarily largely confined to drugs playing a part in physiological processes (endocrine secretions, vitamins, sympathomimetic amines, agents acting on neuromuscular end-plates, and so forth)—an acetylcholine type of pharmacology, so to speak.

It is, however, impossible to teach the therapeutic use of medicines at this stage of the medical curriculum when the undergraduate knows practically nothing about disease processes or patients; nor can one teach the action of digitalis, for instance, on the healthy heart of a normal cat. Applied pharmacology, apart from the use of drugs to illustrate physiological principles, must be taught in the clinical years (45). Yet, in many medical schools, owing to the preoccupation of physicians with problems of aetiology, pathology, diagnosis, and prognosis, therapeutics and clinical pharmacology are often neglected, being frequently only described in the last few minutes of a clinic when, almost as an afterthought, just as everyone is going away, the physician says, 'Oh! and then as regards treatment you will, of course, give . . .' digitalis, penicillin, or whatever it is. Lastly, after qualification many doctors have neither the time nor the inclination to read much about the subject and only pick up an inadequate amount of information about it in the most haphazard way. No wonder modern medicines are often injudiciously used and a bad workman often blames his excellent tools.

It seems then essential that during their clinical years undergraduates should be subjected to continuous instruction in clinical pharmacology, so that they are constantly reminded of the practical applications in man of their basic knowledge, and that such instruction should be an important part of the continuing education of doctors. It is now possible to teach medical students and doctors how to make the most effective and safe use of medicines without asking them to memorize a large number of empirical facts. Much of such teaching is peculiarly well suited to

lecture demonstrations. While it is impossible to teach the feel of a cirrhotic liver or the signs of mitral stenosis save to small groups at the bedside, the treatment of hepatic or cardiac failure can be described just as well to a hundred and fifty students in a lecture theatre as to five in a tutorial, and with a great economy in teaching time.

In recent years the majority of medical schools in this country have established professorial departments of clinical pharmacology or have incorporated senior lectureships in it in their departments of medicine. The clinical pharmacologist has, of course, many other functions besides the educative one: research involving the use of medicines on patients; the organization of clinical trials of medicines; the formation of a link between the laboratories of industry and academic medicine; and, the establishment of close contact with the departments of pharmacy in his hospital group, thereby often effecting considerable economies in the medicines ordered and stimulating their rational use.

It is obvious that the clinical pharmacologist of the future must be a thoroughly skilled physician able to render impeccable clinical service to patients for whom he should be entirely responsible, for it is usually most unsatisfactory to undertake research on other people's patients, being beholden to them and particularly to their medical and nursing staff whose loyalty is primarily to another person. A difficulty in the establishment of such units is how best to provide a proper career structure for those working in them which must necessarily include such interdisciplinary sciences as experimental medicine, pharmacology, biochemistry, and statistics.

Thus, there are solid reasons for believing that in the future medical students will be more thoroughly educated in the use of medicines than they have been in the past. Lack of knowledge about medicines might have sufficed in the old days when a doctor could get by for most of his professional life with a sheaf of prescriptions learned at his medical school and when new pharmaceutical discoveries did not tumble helter-skelter upon each other's heels, but rather advanced in stately progression with intervals (gradually decreasing) for their proper digestion: Salvarsan, insulin, the liver treatment of Addisonian anaemia, and

sulphonamides. No doctor, however well trained as an undergraduate in pharmacology, can hope nowadays to keep up with the rapid advances in that subject without continuing education, especially with the sheer number (the thousands) of medicines on the market.

Such postgraduate education in the past mostly took place in local medical societies in the large centres. Many of them were most venerable institutions. Indeed a plethora claimed to be the oldest of such societies in the country, forgetting that the claims of the Royal Medical Society in Edinburgh were unimpeachable, in spite of being a student sodality. Such societies usually met perhaps twice a month during the winter to hold symposia, to read papers to each other, or to listen to lectures from distinguished visitors. Membership was usually by election and was often somewhat exclusive, being frequently limited to those in least need of postgraduate instruction. Generally the proceedings were awe-inspiring in their dinner-jacketed solemnity and formality, and the discussion of papers was conducted with an impeccable laudatory politeness.

Postgraduate education has assumed a new importance in recent years and centres of such education have mushroomed all over the country, often built by the benefactions of some wealthy philanthropist, sometimes helped by public subscriptions, or even on occasion by the contributions of the beneficiaries; and occasionally by the resources of the local hospital board. A solicitous health service actually gives certain financial inducements to practitioners to keep abreast with the times by attendance at recognized courses of instruction given at such centres. Each of them has its lecture room equipped with every facility for visual and auditory projection, with a library stocked with a selection of current journals, popular textbooks, and deep armchairs in which to pass from the labour of self-improvement to the refreshment of a post-prandial nap, and of course with bars and refectories where between pints and the consumption of club sandwiches advances in therapeutics can be discussed; not frigidly with jealous competitors for private fees as in the bad old days from which we were emancipated by Aneurin Bevan, but with cherished medical colleagues in the battle against disease and with paramedical

colleagues too: the skilled dentist, the beneficent chiropodist, and the increasingly important but sometimes more bucolic veterinary surgeon. Perhaps we may have some optimism as to the future of therapeutics.

Medicines nowadays are exceptional commodities in this country in being produced by the manufacturer, ordered by the doctor, dispensed by the pharmacist, consumed by the patient and paid for by the Government. Usually 'the hand which pays the piper calls the tune', but we must confess that in regard to our clinical practice and use of medicines the Department of Health and Social Security has had till now the most tender regard for our susceptibilities, idiosyncracies, and freedom of choice. Certainly it is uncommon for doctors to be interviewed by the medical officers of the Department regarding excessive prescribing and only a minute number are fined on this account. On the whole this form of control is merely a psychological threat which is rather expensive to administer, but probably justifiable when properly staffed and administered (32*b*). Many doctors are resentful at the degree to which they are solicited and importuned by industry in the process of promoting their products in a manner somewhat reminiscent of Piccadilly after dark in what used to be called the good old days (p. 50). Despite this, however, most doctors are well aware of the vast contribution which the industry has made to the advance of medicine and are deeply grateful for its generous benefactions.

6

The pharmaceutical industry: its economics, profitability, and promotion of medicines

There was a time when physicians and alchemists gathered by the light of the moon herbs and substances which happened to occur in nature and made them into medicines. This duty was soon delegated to the apothecary and later to the pharmacist. With the introduction of synthetic agents in the latter half of the nineteenth century and the gradual replacement of galenicals by them in this century a further delegation in the preparation of medicines has resulted from the pharmacist in his shop to the pharmaceutical manufacturer in his factory.

The great advances in chemotherapy which have occurred in the last thirty-five years have been, with some notable exceptions, largely due to scientists working in the laboratories of industry (p. 16). The vast benefits which modern medicines have conferred upon society (Chapter 3) have immeasurably outweighed their drawbacks (Chapter 4). The pharmaceutical industry, too, seems to possess all the conventional commercial virtues: a high rate of investment; good labour relations; an excellent record of supplying customers during periods of epidemics or individual emergency; a large expenditure of money on fundamental as well as on applied research; generosity in benefactions to public charities and in support of medical, veterinary, and agricultural advancement; and a brilliant record of commercial success which last year contributed £180 million to our export drive. It is, therefore, somewhat surprising that few other industries have been subjected to such adverse criticism, jealous political antagonism, or stringent controls. Apart from the common but rather unattractive tendency which some people have to disparage those more successful and prosperous than themselves and apart from the occasional adverse reactions inseparable from the use of all

effective remedies, the main reasons for the undoubted antagonism which exists to the industry are that its profits are too great because its products are too expensive; that its promotion of medicines is excessive, inaccurate, and exaggerated; and that it battens on human fear, gullibility, and suffering.

Many socialists, trade unionists, and members of the parliamentary Labour Party genuinely believe that the pharmaceutical industry should be nationalized. Their natural partiality to this end is encouraged by a revulsion at the idea of money being made out of the cure of disease, a sentiment still further reinforced by a Left-Wing dislike of all industries actuated by the profit motive, and of this one in particular which is given at least a temporary monopoly by the patent laws. They feel as Mr Laurie Pavitt MP (46), put it that, 'the care of the sick should be taken out of the market place'. It must, of course, be remembered that many others besides the pharmaceutical industry are financially dependent on the NHS which is one of the largest employers in the country: doctors, nurses, builders, food manufacturers, hospital porters, and so forth, all make a profit from the sickness of their fellows, though not perhaps on such a lordly scale.

There are great difficulties and drawbacks involved in the nationalization of the pharmaceutical industry. Firstly, the industry is largely an international one, and subsidiaries of foreign companies (mostly in the USA and Switzerland) are responsible for about two-thirds of the medicines bought by the NHS. Secondly, competitive innovation has been the life-blood of the industry (12*b*). In some future Utopia non-profitmaking motivations may produce the same results without side-effects: till then we must take the world as we find it and remember that since the October Revolution the state-owned industries in the USSR and its satellites have hardly produced a single new medicine of therapeutic importance.

When one reflects on the gambler's risks taken by companies in initiating or terminating research on or development of new medicines (risks which only they can afford to take from the considerable profits resulting from their occasional successes) it

is hard to imagine a government voting millions of pounds of the taxpayer's money to finance ventures which are so extremely speculative. Further, governments, when they have initiated projects, are loathe to confess failure publicly and to be ruthless, as pharmaceutical companies often are, in the prompt abandonment of them: we have examples of this unduly protracted effort in the missile industry with Blue Streak and in the aircraft industry with TSR2 and possibly Concorde. Lastly, there is a real danger that if the search for new medicines was undertaken by a nationalized industry the first relatively effective remedy for a disease to be discovered would be the last one for a long time. Yet the first discovery is rarely the best and, as we have seen (p. 17), it is innovative competition (molecular roulette, 'me tooism') which eventually results in great improvements on the original preparation.

The involvement of the public purse under the NHS started the main criticism of the industry. In its first few years the rocketting escalation of the costs of the NHS (with hindsight it is difficult to understand why this came as a surprise) caused an almost hysterical alarm in governmental circles, but the ministers who had been responsible for the initiation, organization, and administration of the service could hardly blame its structure. The Conservative Party which succeeded Mr Attlee's administration was also in a dilemma, for the NHS, in spite of some drawbacks and the inevitable birth pangs of a hurried delivery, was infinitely superior to anything existing previously and was very popular, especially with the underprivileged section of the public: it would have been political suicide to have tampered with it fundamentally. The part of the service, however, which was not so unassailable was the only sector under private enterprise: the pharmaceutical industry.

Many parliamentarians gained an ill-informed and emotional conception about the industry from the book by Brian Inglis: *Drugs, Doctors and Disease* (47). Inglis drew heavily for his information on the biased Kefauver Congressional hearings in the USA and his obvious prejudices ageinst orthodox medicine did not make him an impartial observer. Information is also derived from

the press, an example of whose contribution on the subject from that daily (48) with the then world's largest circulation read as follows:

> Down the gullet, through the gorge and into the heaving whirlpool of the stomach of the British Public goes such a torrent, cascade, a foaming vertiginous waterfall of drugs, of remedies, of chemical cures, of solid and liquid panaceas that cause the mind to reel and the intestines to writhe and knot themselves into a vortex of abdominal terror.

Parliamentary debate was sometimes a little similar in the turgid histrionics of its expression: thus, Lady Summerskill referred 'to the vultures of the pharmaceutical industry making their unholy profits at the expense of the community' and Mr Harold Wilson, who of course knew perfectly well that the problem of pharmaceutical prices and profits was an extremely complex and difficult one, could not resist the temptation to make the gimmick that the industry 'had grown fat at the expense of the public purse' (49) (in spite of the Voluntary Price Regulation Scheme).

Although our bill for medicines under the NHS has more than quintupled since its inception (*26a*) it has yet remained constant at from 10 to 11 per cent of the total increasing costs of the Service, and represents just over a penny per head per day spent by the public on products which are usually so beneficial. We are yet, however, rich enough to spend eight times that amount on tobacco and eleven times that amount on alcoholic drinks, neither of which is particularly good for us. Though effective medicines are a major factor in medical care, they are as a rule the least expensive part of the health bill. As William Brecon has pointed out we could certainly make greater economies in the NHS if we applied the same rigorous investigative techniques employed on the pharmaceutical industry to hospital buildings, furniture, and equipment on which far greater sums are spent than on medicines; the hospital laundry bill alone exceeds that of hospital pharmacies; but the public and politicians do not get emotionally involved in such prosaic contracts. Lastly, the length of stay of patients under investigation or treatment varies enormously in different hospitals. The expense of a single extra day in a hospital bed is roughly equivalent in most cases to

at least a month's supply of medicines for a patient, but few people bother about the very leisurely turnover of patients in many hospitals.

Though some seem to think so, there is nothing essentially wicked in making a profit provided it is not excessive or derived from monopolies or restrictive practices. The question is how to decide what is a reasonable profit (50). It is one particularly hard to answer when dealing with the pharmaceutical industry (51). Firstly, the international structure of many companies makes it difficult to identify profits earned from the NHS on which industry in this country mainly depends for its sales of ethical medicines, and to find an acceptable formula to allow for overseas development costs incurred by foreign-owned subsidiaries operating here. Being a host country to a number of pharmaceutical multinational companies means that some decisions relevant to our economy are taken outside this country. There is little evidence that this has an adverse effect in terms of monopoly, technology, or balance of payments. In fact this investment boosts real national income considerably. Secondly, the industry is not homogeneous, being composed of numerous firms of different size and activity, often deriving profit not only from ethical and proprietary human and veterinary medicines but also from cosmetics, toiletries, fertilizers, pesticides, soft drinks, breakfast cereals, fine chemicals, plastics, and so forth. The immensely successful pharmaceutical section of ICI, for instance, constitutes only a very small part of that vast organization, and although its profits are accounted quite separately the greater or less success of the whole organization has its repercussions on its members.

It is beyond the scope of this monograph to discuss the mass of figures, tables, and graphs on which the various economic assessments of profitability in the industry have been based (32*c*). Economists of considerable stature express quite divergent views on the subject and seem unable to agree on basic rules of assessment. The two methods most commonly employed in an attempt to ascertain whether profits are reasonable is to express them as a proportion of the capital employed, or to compare them with profits earned in foreign countries. Applying the first method, it would appear that the pharmaceutical industry's return on capital

employed is higher than that of industry as a whole; but this does not take into consideration the fact that in Britain three-quarters of the industry consists of subsidiaries, many of which may be grossly undercapitalized but earning large profits and this often makes figures obtained by this method virtually meaningless. In regard to the second method, it appears almost impossible to make valid comparisons between the profits of a pharmaceutical company in one country with that in another, or the amount of money spent by one country on medicines and that of another. There have been numerous attempts to make these comparisons and it seems probable that the cost of medicines in this country is now (though this was by no means always the case) lower, sometimes much lower, than in other nations of the western world.

Our pharmaceutical industry is probably the most heavily policed by government. Prices are kept tightly in check through the Voluntary Price Regulation Scheme, through which firms negotiate prices with the DHSS. Even so the average cost of a prescription increased by about 10 per cent in 1972 and will probably exceed £1 in 1974 which is nearly double what it was ten years ago. This is not due to the increase in the over-all pharmaceutical price index which has remained remarkably steady in comparison to the rocketting prices of other commodities in our highly inflationary economy: it is due partly to doctors prescribing in larger quantities to save frequent visits and pharmacy charges, and partly to the ready acceptance by prescribers of very new remedies which when new are extremely expensive and constantly replace the old ones in sales volume. It may of course be a wise economy to buy fewer, more expensive, but more potent medicines.

At present the export prices for British medicines are about twice what the NHS pays while imports of medicines into Britain are at NHS prices. It is perhaps not surprising that in other countries importers are beginning to refuse to pay more for their medicines than the exporter can get at home. It is, thus, possible that the Government may either have to increase the NHS price of its medicines or become reconciled to subsidiaries of foreign firms switching production to countries like the USA, Germany, and Japan where they can get a better profit. At present we are

the fourth largest exporter of medicines in the world with the USA, Germany, and Switzerland preceding us in this respect.

The margin between the buying price and the cost of the ingredient is sometimes regarded as evidence in the calculation of excessive profit. Wyndham Davies (*51b*) has illustrated the folly of over-reliance on this yardstick by showing that a bottle of sterile, pyrogen-free, distilled water for injection costs 650,000 per cent more than an equivalent amount of tap water and yet the actual profit from its sale is only 7·1 per cent. More homely examples are the cup of tea made for 1p at home but costing 6p in a café and the sixfold increase on the price which the farmer receives for a cabbage by the time it reaches the housewife.

Owing to the startling increase in the bill for medicines under the NHS the Labour Government in 1965 appointed the Sainsbury Committee (*52*) to investigate the medicines problem, including the pricing, sales, and promotional practices of the pharmaceutical industry. The Sainsbury Committee had at its disposal a greater mass of information and weight of evidence on the economics of the pharmaceutical industry than ever before and its inquiry was thorough and painstaking. In the political climate of the time and the personalities involved, the Committee might have been expected to be highly critical of the industry, and they indeed found some profits on the capital employed to be higher than reasonable, though in some cases it was less than might have been expected. On the whole the Committee did not substantiate unreasonable profiteering by the industry. It was also significant that one of the few firms singled out in their report as showing excessively high profits was the one which for very many years previously had been engaged on a vastly expensive research, culminating in the discovery of the penicillin nucleus, one of the greatest advances in the antibiotic field. It was perhaps not remarkable that between 1963 and 1965, the period under investigation by the Sainsbury Committee, this company should have attempted to recoup themselves for their costly and hazardous expenditure.

Not surprisingly the pharmaceutical industry has done its best to refute the charge that its profits are unreasonable. First, it dwells on the priceless services it renders. These are not in dispute among sensible people and require no further elaboration: the question

is whether these services are excessively rewarded and that, as we have seen, is not easy to answer.

Secondly, the industry points to the vast expenses incurred in research and innovation which have to be recouped (31*b*). There are different interpretations of what is implied by the word 'research', but there is no doubt that the pharmaceutical industry's investment in this type of activity is far greater than that of any other segment of industry. The pharmaceutical industry in Britain supplies the highest ratio of scientifically qualified men: 2·6 per cent against 0·6 per cent for other types of manufacturing companies; and 10 per cent of employees in ethical drug companies are engaged in research in comparison to 0·5 per cent in other industries (32*d*).

Thirdly, the risks as well as the costs of innovation are very great (53). The Hinchliffe Committee (1959), for example, considered that a firm would be quite lucky if it achieved a major therapeutic discovery every ten years. In Britain some 10,000 promising chemicals are synthesized by the industry each year. It is hard to say how many of these are discarded at a very early stage. At most only a few hundred will be put to formal pharmacological testing; of these only a few dozen will be found worth putting to formal clinical trial; and of these only ten or twelve will eventually be marketed. The cost of all this in extensive plant, elaborate equipment, and skilled personnel is immense and the risks of failure enormous. Further, no company could justify to its shareholders the vast capital expenditure and risks of a major research or development programme without adequate patent protection for its discoveries from piratical competitors who have played no part in the discovery of the medicine. In Italy which does not at the time of writing grant patents on pharmaceutical products, few important new medicines have been discovered in spite of the superb technical expertise in that country. Nor has the lack of patents on medicines in Italy made them any cheaper, for there is a general consensus that medicines are more expensive there than in any other country in the western world.

While the industry depends more than any other on patent protection (53) which doubtless involves for some years an element of the derogatory word 'monopoly' (12*d*, 51*c*, 54), it is a

fallacy to suppose that this prevents competition from other firms entering that particular field with a similar though not identical product of their own. In fact patents stimulate competition by abolishing secrecy and making discoveries public. Industry believes that the term of a patent should be extended from sixteen to twenty years rather than reduced as many critics of the system have suggested. For most new patented medicines the time intervening between the grant of a patent and marketing is about five to seven years which leaves it with, say, ten years of profitable competition-free sales, during which the firm will naturally wish to make a considerable profit, much of which will be invested in research to discover a further marketable product. Thus, a short extension of the patent term would not seem to be unreasonable, but it is very difficult to make a judgement on this highly controversial issue. Two learned committees, the Sainsbury Committee and the Banks Committee, who had a great deal of evidence at their disposal differed fundamentally on the thorny question of patent protection. The former believed that there should be a reduction in the present sixteen-year period in order to stimulate price competition, the latter that it should be increased to stimulate the incentive to innovation. In addition to believing that the patent life of a product is too short, industry urges that the success of its research-based innovators is curtailed by the fact that it is far too easy to obtain a compulsory licence under a patent covering a medicine, and strongly advocate the deletion of the compulsory licence provisions contained in Section 41 of the Patents Act.

Besides the risks of unproductive research or failure in innovation the industry is also at risk from what may transpire after a medicine has been marketed. Any number of examples could be given but a single rather famous one will have to suffice: in the early 1930s Lederle established a new plant in America to manufacture anti-pneumococcal serum which undoubtedly reduced the mortality from pneumonia; there were acres of laboratories, stables and animal houses, and a skilled staff, involving a great financial investment. This elaborate venture had only functioned for two years when the discovery of the more effective sulphapyridine (M & B 693) caused it to be completely written off (51*d*).

Then there is the misuse of a medicine by the public, resulting in social problems which may necessitate its withdrawal, as may unexpected adverse reactions which may occur only after a medicine has been on the market for some time and given to thousands and thousands of patients. Further there is the rapid obsolescence of medicines: only a few remain big money spinners for many years.

Lastly the industry points to the fact that though new medicines may be expensive their over-all price has been falling at 4 per cent per annum in recent years. It must be confessed that non-patented medicines fall in price more dramatically after introduction than patented ones. An equivalent dose of penicillin, for example, fell in price between 1947 and 1962 from (in the new currency) 66p to 5p while the semi-synthetic penicillins have only halved in price since 1960. Further, the recent report of the Monopolies Commission strongly criticized the company manufacturing and marketing the popular tranquillizers, chlordiazepoxide and diazepam for making excessive and unacceptable profits from their sale in Britain, an estimated return on capital of 70 per cent where most of the British industry would have been happy with 20 per cent, and that their price had not fallen at all during the seven years in which they had been on the market and protected by patent. The whole matter has a more general dimension and well illustrates the difficulties in accounting the profits of international companies to which reference has been made (p. 42). In order to cope with the variety of NHS and safety standards drug companies have usually had to set up plants in each country. Thus prices vary greatly from place to place and earnings are generated all over the world, but not unnaturally the group's accounting system is arranged to produce the biggest flow of profits by avoiding the heaviest weight of taxation in individual countries.

The pharmaceutical industry, however, is definite that the NHS is not an easy market which encourages high prices: the profitability of industry is far higher in countries like the USA with a 'free market'. In this respect the main safeguard against excessive profits is the Voluntary Price Regulation Scheme which has been operative since 1959 (51*e*). Under it most firms co-operate with the Government by sharing financial information with the

DHSS which can try to satisfy itself and to reassure the public that pharmaceutical prices and profits are reasonable.

After taking all this convincing apologia into consideration the sceptic is still able to point out that losses or even low profits are exceedingly uncommon among major drug companies.

The majority of pharmacists and medical officers in government departments, many academics like professors of therapeutics, and a vocal minority of practising doctors feel that another factor which keeps the prices of medicines and the profits of the pharmaceutical industry too high is the use of brand rather than generic names in prescribing. Some 90 per cent of medicines prescribed under the NHS now carry the manufacturer's brand name rather than the official name of the medicine. The medicines with brand names are usually more expensive (often very much so) than their equivalents with generic names.

The expense of individual medicines is not usually a matter of concern to the patient in the NHS nor often to his doctor. Though firms are required to indicate the price of their product in the advertisement this has not much effect on the quantity prescribed. The doctor chooses the agent he has become accustomed to, often during its patented career and, because its branded name is usually shorter and more euphonious than the official one, he continues to prescribe it regardless of its price.

There is no doubt that generic prescribing would result in some saving to the NHS without usually having a very detrimental effect on the patient. In spite of the fact that the saving would not constitute more than 2 per cent of the drug bill the Sainsbury Committee rcommended that brand names should be abolished and that all medicines, whether the subject of patents or not, should be marketed under the approved official name with possibly the name or trademark of the manufacturer attached to it (*52a*). In coming to its decision the Committee was doubtless influenced by members of the medical profession, many of whom in theory deprecate brand names, though in practice as prescribers they seem to like them very much. The Committee's recommendation was not accepted by the Government.

It would be most desirable to simplify the pharmaceutical Tower of Babel which complicates medical teaching, publication, and practice, and the suggestion that each medicine should have only one name is an attractive one. Official names are also relevant to safety, as it is important for a medicine to be readily and universally recognized. Related medicines may often produce similar adverse effects and a remedy may be prescribed under its trade name without the prescriber realizing its relationship to the one which had previously caused the patient trouble, a relationship to which the brand name gives no clue, whereas the generic name gives some idea of the family to which the medicine belongs.

As usual there is another side to this controversial question for it is not necessarily right to suppose that the active agent, to which the generic name only refers, constitutes the sole basis for the effectiveness of a medicine (12*c*). This is not always the case, since the response to a medicine may also be a function of its pharmaceutical formulation (55). Thus, the extent to which the active therapeutic agent becomes available for absorption is influenced by a variety of compounding factors such as crystal size, disintegration time, diluents, excipients, and other pharmaceutical aids. The nature of these other substances which are mixed with the active agent, the manner in which this is done, and the number and type of quality controls applied at each step of manufacture can affect the therapeutic efficacy of the product. The increasing complexities of manufacture have introduced a plethora of variables that place a strong ethical responsibility on those who provide modern pharmaceuticals. Total quality control is a concept which strives to produce a perfect product by a series of measures designed to prevent or eliminate errors at every stage in production, and the prescription of a well-known firm's branded product, though it may be expensive, ensures that a medicine has a quality on which the manufacturer is staking his reputation. Price cannot be the only consideration. John Ruskin put the matter of price in proper context: 'it's unwise to pay too much, but it's worse to pay too little; when you pay too much you lose a little money, when you pay too little, you sometimes lose everything, because the thing you bought was incapable of doing the thing it was bought to do'.

The producers of generic medicines on the other hand usually only copy some of the more widely used remedies, leaving it to others to produce the rarer, less profitable forms needed by some patients, so that a number of important medicines are still only produced, even after their patents have lapsed, by manufacturers of the original brand-name preparations. As the producers of generic medicines are not burdened by the cost of research and development their products are cheaper than the branded ones but may differ in therapeutic effect. These differences are not very often important but it is dangerous to assume that generically equivalent products are invariably of equal therapeutic potency to branded products. Lastly, it is difficult to imagine (as the generic name refers only to the basic chemical ingredient) how the very numerous compound preparations which flood the market could be given official names, especially when any attempt to do so could immediately be stultified by the manufacturer making a slight change in the formulation. Indeed if generic non-equivalence can cause therapeutic confusion and potential danger with a tablet containing a single agent it is easy to see that the problem is vastly magnified in the case of compound preparations containing a number of active ingredients.

Advertising is an essential: all new things require in this way to be drawn to our attention (32*e*). Doubtless it is a wasteful procedure for, as Lord Leverhulme said, 'probably half of every advertising appropriation is wasted, but nobody knows which half'. If advertising, which costs the pharmaceutical industry in this country about £13 million a year, were stopped completely it might have the immediate effect of lowering the cost of our medicines bill by 1 per cent, but ultimately would be uneconomical for had it not been for the marketing techniques so often bitterly assailed few of the medicines on which modern medical practice is based could be afforded at all.

In the unlikely and probably undesirable event of the industry being nationalized (p. 39) it would none the less have to continue to advertise like the gas and electricity industries and the Milk Marketing Board do. The industry is accused in the western

world by the medical profession of spending too much on anti-social sales promotion, but the complaints of doctors here are exactly the reverse of those in Russia (12*f*) where the advertising of pharmaceuticals is forbidden: there they complain that they do not hear about the introduction of new medicines quickly enough and are inadequately informed about them so that an excessively long time may elapse before old-fashioned remedies are replaced by more efficient modern ones.

It is only necessary to look at the fantastic claims made for remedies in Victorian and even Edwardian newspapers and magazines to realize how the advertising of proprietary medicines has improved in the last half century under the influence of the Proprietary Association of Great Britain and the IBA which have adopted voluntary codes for the promotion of over-the-counter remedies. The advertising of such medicines can perhaps be a more serious problem than that of ethical ones for though they are relatively innocuous their abuse by the public can have very serious consequences such as analgesic nephropathy (56). Further, proprietary firms may sometimes be less scrupulous than the manufacturers of ethical remedies about their advertisements, the readers of which are not always educated professionals.

It can also be said that the standard of advertising of ethical medicines to the medical profession has improved in recent years. There was room for improvement as in the past it was not infrequently so loud, brash, and vulgar as to jam the channels of communication. Even now it is occasionally subject to justifiable criticism in the matter of good taste, being sometimes more appropriate to cosmetics than to the more serious subject of ethical medicines, and doctors make much of their distaste for it, deploring its character, quantity, and commercialism. Nevertheless, as Garai (57) has said, it would be a great step forward if doctors realized that their high opinion of themselves is not shared by writers of ethical drug advertising. We should stop bemoaning this attack on our professional maturity and begin to realize how thoroughly justified it must be for no advertising which does not work will continue to run. No ethical medicine can reach the market save through our intermediary and the market is always sensitive to sales curves. Let the sales of any product decline sharply and

remain down and that product will die. Let doctors but withhold their approval of new medicines until they are satisfied with the candour, accuracy, and scientific completeness of their advertisements and until good evidence has been provided of the claims made for them and it will cease to be economically feasible to market medicines without such evidence. Doctors have the sole and absolute power to determine sales of ethical medicines and if they express their wishes on prescription pads their wishes will be heeded quickly.

Perhaps doctors are justified at resenting the quantity of advertisements (up to seven a day) they receive by mail. Such promotion and that in the medical journals is not very educational but rather just a means of impressing by frequent inculcation or admonition. On the other hand they have only to request on a postcard to the Association of the British Pharmaceutical Industry that they should be taken off the mailing list for this importunity to cease, but few of them evidently think that the harrassment is so significant that they take the little trouble to do this. Besides a learned profession should be more able to assess the worth of an advertisement than a housewife for a detergent.

The data sheets which must now accompany all product licences (see p. 76) and to which all subsequent advertisements must conform may do much to improve the standard of promotion and to eliminate excessive claims. The very stringent control of medical advertisements by the Food and Drug Authority in the USA to ensure that the truth, the whole truth, and nothing but the truth is told in them has perhaps caused such advertisements to become excessively detailed (p. 85).

The industry spends a large part (some 45 per cent) of its advertising budget on promotion by representatives who call upon doctors. Most of the latter are preoccupied, conservative, and proud but, as Teeling-Smith has said, 'they should be the first to recognize that there is a very narrow margin between a stimulant and an irritant' (26*b*). Many doctors seem to have an exaggerated feeling of outrage about such calls by detail men. This is often unjustified and in some cases may even be contrary to the doctor's best interest. Nevertheless, their irritable, unkind, and occasionally ill-mannered reaction to a call by a representative is

understandable enough when they are frantically busy, worried, and rushed. This is especially the case should the representative happen to be brash, prolix, pretentiously pseudo-scientific, and claiming what is exaggerated and difficult to substantiate. Such detail men, however, are relatively few and seldom survive long in their job. Provided he is an intelligent, diplomatic, and pleasant fellow he can play an important and useful role in introducing new products to the medical and pharmaceutical professions by giving information about their use, cost, and availability.

Valuable products should not be kept secret nor should manufacturers just have to hope that doctors will stumble upon them from conversation with their colleagues or from their reading of medical journals or presence at medical meetings which they sometimes fail to read or attend. Well-briefed detail men, because of the specialized information they can bring are not without value to the busy practitioner or pharmacist. They are also a valuable channel of communication from the medical man back to the company.

In conclusion it should be apparent from what has been said that the problem of the economics, profits, and ethics of the pharmaceutical industry and the promotion of their products is not a simple but a very complex one. Those people who see everything clearly as black and white and who are quite definite about what is right or wrong are in many ways enviable. With their evangelical zeal they are the people who do most good in the world—and the most harm. On the other hand those who pride themselves on being more civilized, who find it difficult to answer most controversial problems because they realize how much there is to be said on both sides, may become like that wretched ass which starved between two bundles of hay because it could not make up its mind whether to turn to the one on the right or that on the left. The study of the very considerable literature which has accumulated on this matter may result in an unprejudiced reasonable man coming to the following conclusions.

1. Pharmaceutical firms, though there is a wide scatter between companies, over-all consistently make significantly higher profits

than other industries. This has little to do with the existence of the NHS in this country. The high profits earned are probably justified by the immense costs of research, innovation, and promotion, the great risks undertaken and the early obsolescence of the products. Sometimes a medicine may be cheap at any price if it saves months of invalidism and the costs of hospitalization or medical expenses. What is the cost of a life?

2. As one learned committee believes that the length of time in which a new product is given patent protection should be decreased whereas another equally learned one believes that it should be increased, a reasonable man may be pardoned for feeling that the current sixteen years is about the right time. The total removal of patent protection from pharmaceuticals would not result in lower prices.

3. The industry is an example of imperfect competition, being to a slight extent monopolistic and partially freed from pricing medicines according to the ordinary forces of supply and demand. Viewed as a whole, however, firms are in fierce competition with each other because product substitution rather than price is the competitive force. The Hinchliffe Committee commented with justice 'that there must be few industries in which a market can be lost as quickly as in the pharmaceutical industry'.

4. It would be extremely difficult and undesirable to nationalize the industry. The same can probably be said for the abolition of brand names.

5. Advertising is an inescapable and valuable activity of all industries and much of the criticism of the pharmaceutical industry's promotion of medicines is unjustifiable. The number of advertisements reaching the profession by mail, however, is probably excessive, and some of the glossy advertisements in the journals lack good taste.

6. No profession or industry lacks its quota of black sheep. Doubtless the pharmaceutical industry is not exceptional in this respect but it might be claimed for it with some justice that it has as high or higher a proportion of intelligent, educated, altruistic, and idealistic men in it than in most other industries.

7

The testing and evaluation of new medicines

The introduction of new therapeutic agents to medical practice is preceded by long and laborious investigative exercises which may fail at many stages. Great numbers of chemicals which seem likely to affect a particular pathological condition have to be screened by organic chemists. Those judged worthy of further study are then subjected to detailed toxicological and pharmacological investigation on animals (31*c*). They all require acute toxicity testing which consists of the administration to animals of large single or divided doses over a short period of not more than twenty-four hours. Almost all of them also require chronic toxicity tests, the length of which varies according to circumstances from two or three weeks to perhaps two years. The tests should also reveal the presence or absence of a species difference so that a variety of animals are included in the trial and, if a species difference is noted, the application of the chemical to man must be the more cautious. Apart from giving some clue as to the toxicity, dosage, pharmacology, and pathological effects of a new agent, animal tests are of some help (often rather limited) in determining its teratology and carcinogenicity, and its efficacy in those infections and diseases which can be experimentally induced. The screening and testing necessary to put twenty chemicals on the market a year involves the use of well over a million small rodents and about 16,000 cats or dogs.

Quite early in the course of the evaluation of a new chemical after the early toxicity tests have been carried out but before a full-scale pharmacological investigation of the product in animals is embarked upon, it is essential to give small quantities of it to a few healthy human volunteers, not to test its pharmacological actions nor, of course, its therapeutic efficacy but simply to determine its absorption, metabolism, and excretion in man which may

be very different from those in animals. It is often difficult to find adequate numbers of volunteers for these studies. In Britain they usually consist of technicians and scientists in the laboratories of the industry and occasionally medical students. In addition to these, long-term prisoners are often used for this purpose in the USA. Laboratory workers are sometimes subjected too frequently to such experiments, being thereby exposed to too many chemicals to which they may become sensitized. Further, it is conceivable (and this also applies to medical students) that they may be subject to undue pressure to 'volunteer' or may do so to ingratiate themselves with their superiors.

It is difficult to imagine the public in Britain agreeing to the employment of prisoners for this purpose which is a pity. Provided the most scrupulous care is taken to see that there is no element of coercion in their volunteering; that as in the case of other volunteers the experiments to which they are subjected should involve a minimum of risk or suffering; that they should not be used for more than one experiment; and that they should not be able to purchase in this way earlier release; then the rigidly controlled healthy prisoner is ideal for this purpose. Prisoners are usually only too happy to volunteer, for there are financial and other reasonable compensations for serving as subjects which are entirely warranted and (though it may be ingenuous so to believe) some prisoners genuinely feel that in this way they are assisting in their own rehabilitation by paying back some of their debt to society.

While extensive experiments on animals are an essential preliminary to the clinical trial of a new medicine on patients it is well recognized how difficult it is to extrapolate their results to man. A great species difference exists in the reaction of animals to medicines and man is a distinct species. His subspecies may also vary enormously in their response to medicines. Some medicines which are extremely toxic to animals are harmless to man and vice versa. A number of our most valuable products including digitalis might never have reached the pharmacopoeia had the preliminary pharmacological requirements now insisted on been then necessary. For example, it is unlikely that quinine would have been approved for clinical trial had it been previously

tested on dogs who are exquisitely sensitive to it and go blind after quite a small dose. There is a danger nowadays that tests of drugs on animals are sometimes being unduly protracted because of the rigid requirements of the controlling authorities.

Clinical trials are usually conducted by physicians with a special interest in the disease for which the new medicine is intended, but the information derived from them is often disappointing. The fact that a physician may be an international authority does not necessarily imply that he has the training in experimental pharmacology, statistics, and biochemistry to enable him to design and carry out a clinical trial of a new medicine which will give meaningful results. The case for clinical pharmacology rests on the need to provide special skills and personnel to conduct such studies. It need not deny a useful role to the experienced physician interested in studying medicines in a special field: after the primary trials carried out by a clinical pharmacologist on a very few patients, there is need for a much wider dissemination of the product to gain experience of its efficacy and to detect less common but possibly more serious toxic effects. Such trials require clinical experience and accurate record keeping but need not demand the special skills required for the primary trials.

The controlled clinical trial which was developed by Sir Austin Bradford Hill about 1945 is almost exclusively an English contribution to medicine (58). Though a good controlled nutritional experiment is described in the first chapter of the Book of Daniel, and in the middle of the eighteenth century James Lind studied the treatment of scurvy in a remarkably modern manner, the use of controls is a recent development. The word 'control' was not used in medical literature until 1890 and it has only been in the last twenty-nine years that modern medical science has conducted clinical trials of medicines within a conceptual framework, constantly tested by accurate observation and statistical analysis, and in which plans are made to eliminate bias in allocation and bias in evaluation.

Clinical trials themselves are, of course, as old as medicine. Unsuspecting patients have been exposed since the night of time

in ordinary practice to uncontrolled experimentation with unproven drugs or to relatively untried surgical procedures. When the first doctor decided to ring the changes in treatment from the fillet of a fenny snake to the eye of a newt or the toe of a frog and to observe the result it constituted a clinical trial. A question was asked of Nature and impressions followed: haphazard impressions, greatly influenced by the dogma of traditional teaching. Thus the clinical impression persisted for hundreds of years that bleedings, sweatings, vomitings, and purgings were beneficial and it took aeons of time before the better remedies drove out the worst. Random experiments by thousands of doctors on millions of patients produced practically no positive results.

Even in the earlier part of this century undesirable therapeutic fashions persisted for prolonged periods before they were abandoned. Thus, in 1924 injections of gold were introduced for the treatment of tuberculosis and remained fashionable for fifteen years though they did a great deal of harm and it is very doubtful whether they had any beneficial effect on that disease. In contrast when modern anti-tuberculous medicines became available, well-designed trials proved their efficacy in fewer months than it had taken years to prove the worthlessness of 'Sanocrysin'. Then again, in the early part of the century that great surgeon, Sir William Arbuthnot Lane, did not stick to his last but as he became older wandered off into more recondite fields where he discovered the colon as the nigger in the woodpile of health, as a sort of septic tank which an unwise deity had inserted into man. In consequence a fierce and prolonged Indian summer of purgations, bowel wash-outs and even, on occasion, colectomy ensued in an effort to eliminate intestinal toxaemia then thought to be one of the chief causes of ill-health; and for many years children lost their tonsils and adults their teeth in the sacred cause of the eradication of focal sepsis. In contrast, modern controlled trials are producing benefits to mankind at an ever-increasing rate and can claim to be among the great therapeutic advances of the last quarter of a century.

Nevertheless, there is a widespread feeling among the public and even among some doctors that the medieval type of clinical trial which has been mentioned and which persisted till about

thirty years ago was ethically more acceptable than a carefully planned trial in hospital, especially if the latter is conducted by a clinical university professor who is occasionally regarded as being totally lacking in clinical judgement, common sense, or compassion. Such trials are apt to be looked upon as treating patients like guinea-pigs and questions may be asked in Parliament about them. Incidentally, what would we have thought today of the ethics of that quiet country practitioner, Edward Jenner, who has been regarded with reverence as the pioneering hero of preventive medicine? Having heard that dairymaids who had had cowpox seldom suffered from smallpox, he vaccinated a little boy with material from the hand of an infected dairymaid and then eight weeks later had the temerity to inoculate the child with the dreaded infection of smallpox. The child's immunity proved the value of the procedure, but had he died as the result of it Jenner would certainly nowadays have faced the possibility of a life sentence.

There must always be some patient or group of patients who receive a new medicine for the first time: it is surely desirable that this should happen under careful observation in hospital and that the experience of such patients should be made of value to their successors.

The advances in therapeutic knowledge made before the development of the controlled clinical trial took place as we have seen at infrequent intervals (p. 57). Progress in therapeutics cannot now afford to wait for such relatively rare advances in human knowledge and the need for the accurate assessment of medicines has never been greater than today. Those doctors who were so fortunate as initially to have been testing insulin, liver extract, the sulphonamides, and penicillin had a relatively easy task as the value of these agents became immediately apparent without carefully designed trials to prove their efficacy. More often, however, the problem nowadays confronting the clinical investigator in this field is to find out whether a new medicine reduces the mortality from a certain disease from, say, 10 per cent to 5 per cent. Without extensive and carefully planned controlled trials this is impossible and even then, as in the case of anti-coagulants in myocardial infarction, it may be very difficult.

Clinical trials usually employ one of the following techniques:

(*a*) The construction of two or more closely similar groups of patients by a process of random allocation.

(*b*) The comparison of these groups on different methods of treatment.

(*c*) In some cases it is possible to give all the treatments under comparison to one group of patients acting as their own controls.

(*d*) The active treatment of one group by the agent under review is controlled by another group receiving no treatment at all, though the latter may be given an inert placebo for its psychological effect.

(*e*) In most trials the patient does not know the treatment being given so that the trial is for him 'blind', but sometimes the doctor does not know either so that the trial is 'double-blind'.

Clinical trials of this nature usually involve questions of ethics. These were admirably discussed by Professor Witts whose views on the problem have largely inspired these reflections (59). A code of humane ethics has been built into our British medical profession through the ages and its standards are certainly not lower and may be higher than in other countries. There are black sheep in every profession but it is exceptional to find them among those who have risen to be consultant hospital physicians, the sort of people who would be in charge of clinical trials. It is highly unlikely to find among them wicked, unprincipled, or heartless men. There is apt, however, to be a considerable difference between the physician-friend and the physician-researcher. The former has a personal relationship with his patient, sharing his distress and anxious to alleviate it. Objective experimentation to confirm or refute some biological generalization is apt to be foreign to this relationship, and there is always a danger that medical research workers may have a slight tendency to regard their patients as experimental 'subjects', though this must be exceptional.

It is not surprising, therefore, that various authorities have attempted to draft codes of ethics to govern human experimentation: the Nuremberg Code, inspired by the trials resulting from

the ghastly human experimentation in the Nazi concentration camps; the code in the Report of the World Medical Association; and that of the British Medical Research Council. While it is possible to enunciate some very broad rather platitudinous principles which are really intrinsic to the medical ethic, it is doubtful whether precise rules can be framed applicable to all the immensely varying circumstances of clinical trials, about which it is so easy to generalize and so difficult to particularize. It is true that those promulgating these codes have said that they are only guides to doctors; but once formulated it is difficult and, even legally hazardous, to diverge from them. A rigid ethical ideal may be too restrictive when facing real-life problems.

For example, one of the general principles on which most codes insist is that the nature, purpose, and risks of the trial should be explained to the subject of it, who should of course have complete freedom to decide thereafter whether or not to participate. On the face of it this code sounds very reasonable and it is usually observed. Nevertheless, it is often quite impossible to give a patient (especially one poorly educated) a proper understanding of what is involved, and nothing less is of much value. Just to ask him if he minds if some new tablets be tried out on him (to which he will always give his consent if he has any trust in his doctor) might simply be an excuse for the investigator to divest himself of the ethical decision as to the propriety of his experiment. When a comparison is being made between two products, either of which as far as the doctor knows may be equally efficacious, it seems unnecessary to obtain the patient's consent. After all, a doctor in practice does not usually seek his patient's consent before prescribing a new remedy or reverting to an old one. Because of the profound effect of psyche on soma there are some trials which would be ruined if the patient understood the nature of the experiment or even that he was participating in one. Lastly, the patient's consent is surely superfluous in therapeutic trials on conditions hitherto invariably fatal such as leukaemia or inoperable malignant disease. Under such circumstances any treatment carrying the faintest chance of benefit is justifiable.

Another principle of most codes which sounds so reasonable and is usually right lays down that it is unethical to include in such

trials mental defectives, lunatics, or children in institutions not under the care of their relatives, as such persons are not free agents. Though this may not be intended, the strict adoption of such a code excludes experiments in different types of institutional care, in the treatment of maladjustment and many clinical trials in psychiatric therapeutics. Again, a strict interpretation of this code would declare as unethical experiments on children to discover, in the very circumstances in which it is important to do so, whether, for instance, pasteurized milk promotes health and growth as well as raw milk, to what extent the sugar in the institution's diet contributes to the incidence of dental caries or whether gamma globulin is more or less effective than convalescent serum in the prevention of measles.

Thus, as Sir Austin Bradford Hill (who has done so much for clinical trials) has said, instead of laying down rigid rules to govern experiments on humans, a series of questions should be posed in the specific setting of the particular trial envisaged. It is probable that his six questions and his sensible answers to them cover most of the ethical problems involved. It would take too long to describe them in this monograph but the reader who wishes to pursue the subject further would do well to consult his article (60).

In conclusion it may be said that the ultimate judge of what is justifiable is not a rigid code of rules but the conscience of the doctor concerned which should be a tender one and the consciences of his colleagues, for in each hospital where such trials are conducted there should be an ethical committee which he should always consult as to the propriety of his actions. The responsibility of precluding unethical human experiments must lie with the medical profession rather than with the law. Much can be done by medical societies at their meetings in criticizing an over-zealous or unscrupulous investigator, and by medical journals in refusing on this account to publish his papers. The end does not always justify the means and the good things a man does can be made complete only by the things he refuses to do.

The clinical trial of a new medicine will, of course, provide for the record of its adverse reactions, for no matter how meticulous the preparatory work of the pharmacologist and clinician may be there is ultimately no substitute for years of experience of its use in practice. For example, the medicine might cause a very serious or fatal toxic reaction in 1 in 1,000 patients which would constitute a grave drawback to its practical use, yet such a reaction might never have been encountered even in an extensive clinical trial before marketing. Thus, in addition to its pharmacological testing and clinical trial the monitoring of its adverse reactions after marketing is a third important part of the evaluation of a new medicine. While the recording and notification of adverse reactions to their products is an essential function of all firms, the main responsibility for monitoring such reactions has devolved on official control agencies.

For this reason some countries have established voluntary or statutory monitoring systems to detect and investigate adverse reactions to medicines after they have been marketed. Probably the first example of this type of effort was the American Medical Association's Registry of Blood Dyscrasias started by Max Wintrobe and Philip Sturgeon in the early 1950s. Certainly the paramount importance of putting adverse reactions to medicines on a proper epidemiological basis is now increasingly realized: so that the benefits conferred by medicines can be balanced against their ill effects; so that an informed precise choice can be made between one product and another; and so that the desirability of medicinal treatment can be compared with that of surgery, radiotherapy, or no treatment at all. Thus, the collection, tabulation, and analysis of the adverse effects of medicines on a national and international computerized scale is likely to be of inestimable value to doctors and the community (61). Ultimately the success of all reporting systems must depend on the co-operation of the medical profession which must be voluntary for, unlike the reporting of notifiable diseases, the reporting of suspected adverse reactions does not lend itself to compulsion.

Reports of adverse reactions must bear some relationship to the extent to which a medicine is used. Without this as a denominator the numerator, the number of its reported toxic effects, is virtually

meaningless. In the UK we are in a better position than in most countries to know how much any particular medicine is used as all prescriptions written under the NHS become eventually available for analysis so that its consumption is fairly well known. It is only possible to make rough approximations of the relatively small quantities prescribed in what still remains of private practice, of what is used in hospital or of domestic proprietary remedies purchased by the public without a prescription. Some estimation, however, of the consumption of such medicines can be made by the use of commercial market research facilities.

The majority of national monitors, including that employed in the UK by the Subcommittee on Adverse Reactions of the Safety of Medicines Committee (p. 72) depend mostly on random reporting (62). Large volumes of reports are handled and automatic processing of data is required so as to enable the personnel responsible for scrutinizing the data to identify problems as early as possible. There are some serious defects in monitoring systems based on random reporting. Firstly, while the majority of doctors associate incidents such as jaundice, rashes, or blood dyscrasias with drug therapy, they may not suspect such relationships with other manifestations as they do not expect the unexpected. Consequently the monitor may be insensitive as a means of detecting such hazards. Secondly, reactions are grossly under-reported and constitute no more than the tip of an iceberg most of which remains submerged beneath the surface of our awareness. Thus, in 1966 at a time when medical and public interest was greatly concerned with the dangers of thrombo-embolism in women taking contraceptives, only 15 per cent of the deaths due to this cause were reported in Britain to the Subcommittee. It is certain that the reporting of adverse reactions to other medicines not under the same public scrutiny must have been much less complete and that many unexpected ones are not identified at all by random reporting. It serves, however, to pinpoint suspected problems which can then be more thoroughly investigated, and if one or two individual clinicians have a sudden inspiration or 'hunch' that an incident may be due to drug therapy and report this to the centre, the latter has facilities to test their hypothesis

or to delegate responsibility for investigating it further to specialists in the appropriate discipline.

Most serious or fatal reactions are rare. In general the more serious the reaction the rarer it is and the larger the study required for its evaluation. Such reactions are, therefore, unlikely to be detected by monitors set up in individual hospitals or groups of hospitals and require for their detection national or international monitoring systems drawing experience from thousands of doctors and millions of patients. On the other hand, hazards of lesser severity but greater frequency may be better evaluated by intensive monitoring in hospitals where both the reaction and quantity of the medicine used can be accurately measured. Continuous hospital monitoring schemes tend to be expensive to operate and motivation and efficiency may be difficult to maintain in view of the comparatively small chance of success in identifying a new drug safety problem. The specialized skills and equipment available in hospitals are best employed on the investigation in depth of hazards identified elsewhere, rather than in attempting to detect previously unrecognized hazards.

Other applications of epidemiological techniques in this field employ sampling of prescriptions and prospective studies of patients who have received certain medicines in hospital or in general practice (drug-based studies) or on populations of patients suffering from particular disorders (disease-based studies). Less frequently, and only when minor reactions are involved, studies may be conducted on individual patients who have themselves exhibited reactions (re-challenge studies).

There would be no point in maintaining a system for detecting and investigating the hazards of medicines were the results not communicated to the medical profession as early as possible even though they have not been fully evaluated. The publication of suspicious associations between medicines and reactions has the additional benefit of often leading to more complete reporting. When a single bird is flushed and fired at the rest of the covey often gets up. Thus, programmes for analysis must include provision for signalling early warnings whenever the evidence for a

causal connection between a medicine and a reaction passes a selected threshold. An unfortunate repercussion of such early warnings may be the considerable, sometimes unnecessary and often sensational, attention they attract in the lay press. This is particularly true of the reports of the complications associated with the use of oral contraceptives. The risk, however, of causing unnecessary anxiety to patients who may read about drug hazards is usually outweighed by the risk of withholding such early knowledge from the profession; and perhaps it is no bad thing to instil a healthy awe of medicine nowadays.

In some instances the most effective way of drawing the profession's attention to a new but rare hazard is to encourage the reporting doctor to publish his findings in a medical journal of wide circulation. In others it is best to ask the manufacturer concerned to inform the profession and to revise the promotional literature. Occasionally it may be necessary to recommend at a national level that restriction should be imposed on the use of a medicine. For example, it may be desirable to stop direct sales to the public, to advise use only under laboratory control or to recommend that the medicine should not be used by certain types of patient such as women of child-bearing age. Medicines of low efficacy or high toxicity may be withdrawn on the recommendation of the national monitor if more effective or less toxic remedies for the same condition become available.

When a drug history has become an established routine, an integral part of clinical history-taking, a significant advance in monitoring adverse reactions to medicines will have occurred.

8

Regulatory controls of medicines in Britain

Democracy has always sought the ideal of ordered freedom within the law with the force of sanctions in the background (a condition in which authority and freedom are blended in due proportion and in which the state and the citizen are complementary to each other) a sort of age of Pericles (63). Yet democracy is a very difficult form of government and it was foolish to expect underdeveloped countries to adopt so easily what took us hundreds of years to evolve. Democracy requires constant guarding from slipping in one direction into chaotic licence, due to the relaxation of laws on such things as capital and corporal punishment, gambling, pornography, homosexuality, abortion, and divorce, or in the other into bureaucratic tyranny from the gradual erosion of individual liberties by governmental action. For example, the law of supply and demand and the devil take the hindmost (the economic rule of the jungle, beloved of Victorian ironmasters) became abhorrent to most humane people but, in attempting to mitigate its asperities it becomes difficult to find another logical alternative short of Communist state control (the rule of the ant-heap) which most of us do not like very much either. Between these two extremes, reforms, no matter how salutary, are bound to be hurtful to and resented by some, and may sometimes create further problems more formidable than the abuses they have sought to remedy. Thus, the disastrous results of attempting to impose prohibition of alcohol in the USA are well realized. In the same way the apparently very necessary measures to control the prescription and production of modern medicines might possibly become, unless they are regulated with great wisdom, the thin edge of the bureaucratic wedge to professional and industrial freedom. The trouble is that although we nearly all maintain that freedom is good and restriction bad, yet

when someone else's freedom of action becomes inconvenient we usually clamour for its restriction, a restriction which then seems essential in the public interest and based on the purest of motives: 'The Government must do something about it' we say. Such restrictions are apt to be particularly undesirable when imposed hysterically to meet a crisis.

Modern medicines are such potent weapons (powerful for good but also for evil) that there is a general consensus that the sole responsibility for their production and use can no longer be left entirely to the manufacturer and prescriber. Yet it is very difficult to know how far the Government should attempt to control their production and prescription without undue interference with the advance of scientific therapeutics, the well-being of the pharmaceutical industry, the right of the ordinary man to buy simple remedies for himself in a multiple store and the cherished freedom of the doctor, dentist, or veterinary surgeon to prescribe what he thinks best for his patient, though it is a little doubtful whether the responsibility which the professions have shown in the use of modern medicines entirely justifies that freedom. It may be rather surprising to some that the situation was perhaps best put by that remarkable man Aneurin Bevan:

> Any health service which hopes to win the consent of doctors must allay the fear that bureaucratic interference will affect professional freedom and come between the doctor and his patient. There is no alternative to self-government by the medical profession in all matters affecting the content of its academic life. It is for the community to provide the apparatus of medicine for the doctor. It is for him to use it freely in accordance with the standards of the profession and the requirements of his oath.

Attempts at some form of control of medicines have gone on in this country for a very long time. The earliest efforts were the catalogues of medicines or herbals, providing descriptions of poppies and mandragora, of mercury and antimony, and of preparations made from the bodies or excreta of animals, to help physicians to recognize and use these agents. Though his head might be cut off if the results of their administration were dire,

the physician was not then summoned under the provisions of any Act. From these early herbals grew the London and Edinburgh *Pharmacopoeias:* essentially herbals themselves but given authority by their respective royal colleges. The Gin Acts of the eighteenth century first recognized that government had some responsibility to prevent the adulteration and abuse of a drug, but until 1864 when the first British *Pharmacopoeia* was published there was little real control over medicines in the UK. Indeed the counters of pharmacists' shops were piled high with opium pills and their shelves with jorums of laudanum, freely offering for a few pence oblivion to those pouring out of the dark satanic mills of the Industrial Revolution. Nevertheless, though some opium-eaters resulted such as de Quincey, Coleridge, and Bramwell Brontë, British people on the whole preferred to seek their solace with Bacchus in Hogarthian gin palaces, rather than with Morpheus the bringer of dreams.

The British *Pharmacopoeia* (64) has enjoyed an international prestige, though till recently there have been inadequate means to enforce the quality control of medicines which its numerous editions and their addenda have enjoined. We have come a long way since 1864 in laying down standards to try to ensure the purity and strength of medicines and to prevent their adulteration, abuse, and misdirection. During the last hundred years British governments have been active in establishing these standards and there has been a progressive widening of such efforts throughout the world so that nowadays a patient can have at least some confidence that he will be supplied with the same agent whether he purchases it in London, Paris, New York, or Tokyo. In the so-called more spacious days it sufficed if he always bought his infusion of digitalis leaves from Mistress Ford rather than from her rival Mistress Page down the street whose brews might differ like the strength of a cup of tea in different homes.

The Dangerous Drugs Acts recognized the danger of drug addiction and controlled the manufacture of certain drugs by licence together with a strict recording of their sale and supply. In consequence, the incidence of addiction to potent narcotics was

so rare in Britain as to be a matter of almost incredulous envy in other countries. In 1950 there were only 333 known addicts to hard drugs (heroin, morphine, pethidine, and methadone) in the UK; and these were mostly elderly therapeutic addicts and a few doctors, nurses, dentists, or pharmacists who had ready access to these agents. Unhappily, during the last thirteen years their number has increased by at least tenfold and the new addicts are mostly young delinquents. The Misuse of Drugs Act (1971) has in consequence proved necessary (p. 76). The Cancer and Venereal Diseases Acts prevented the deception of the public by advertisements of quack nostrums for the treatment of serious disorders. Various Pharmacy and Poisons Acts elaborated control over the sale and supply of certain potent medicines, and the Therapeutic Substances Acts controlled agents such as vaccines, sera, and hormones, the purity and potency of which could not be established by chemical means.

This mass of legislation (65) was achieved within the context of a bewildering number of statutes in need of consolidation, while the number of organizations with varying degrees of authority over medicines (some reporting to the Home Office, others to the Ministry of Health or Agriculture, the Board of Trade, the Privy Council, and so forth) made our legislation on medicines somewhat chaotic. Nevertheless, it served its purpose satisfactorily till the explosive introduction of powerful new remedies in the 1940s and 1950s proved it inadequate to cope with modern conditions.

Though we had been well aware for years of the toxic nature of many of the medicines we were using we had been curiously complacent about them and until 1968 no statute in the UK required the pre-marketing approval of medicines on the grounds of their safety. Apart from those biologicals listed under the Therapeutic Substances Acts, anyone could market any product, no matter how dangerous or inadequately tested, without seeking official approval. It took the emotional reaction to the thalidomide disaster to galvanize us out of our somewhat *laissez-faire* attitude. Following it the Ministers of Health established the Safety of

Drugs Committee in 1963 as an interim measure till the more recent comprehensive legislation on medicines could be enacted and become operative (p. 73). It was a purely voluntary arrangement, official only in the sense that its members were appointed by the health ministers who also provided its finance, accommodation, and secretariat. It consisted of eleven very part-time, originally unpaid, scientists, physicians, and pharmacists, assisted by a small staff of civil servants, consisting to begin with of only six doctors (four recruited from industry on the principle of turning a poacher into a gamekeeper) and two pharmacists. The staff did most of the preparatory work but, although they were the most valued servants they did not become the masters of the Committee who took full responsibility for the ultimate decisions.

In spite of the complete absence of legal sanctions (there were, it is true, some unofficial ones), manufacturers were quite glad to share some of the responsibility for the safety of their products with an independent body. Thus the Association of the British Pharmaceutical Industry and the Proprietary Association of Great Britain promised, before the Committee started to function on 1 January 1964, that none of their members would (*a*) put a new medicine to clinical trial or (*b*) market a new medicine without the Committee's approval: a promise loyally observed.

The Committee did not itself undertake pharmacological tests or clinical trials of medicines: the responsibility for these remained firmly with the manufacturer; it simply evaluated the manufacturer's submissions on their tests and laid down certain standards for them. Its remit eliminated cost or the comparative efficacy of medicines from their deliberations except in so far as their safety was concerned. Thus, a considerable degree of toxicity might well have been acceptable for one which stayed the progress of cancer, but one used for a trivial disorder would have had to be relatively innocuous. Therefore, the clearance of a medicine for marketing did not necessarily imply the Committee's approval of it as a therapeutic agent but only its reasonable safety for its intended purpose. Although the safety and efficacy of medicines are often inextricably entwined, efficacy *per se* was not the function of the Committee.

To undertake its responsibilities the Committee developed three subcommittees (the first two eventually merged) to advise them in their decisions; the first, to scrutinize the adequacy of the pharmaco-dynamic studies undertaken on the medicine before its clinical trial on patients was permitted; the second, to scrutinize the adequacy of the clinical trials on it before marketing was approved; and the third, to monitor its adverse reactions after marketing and to feed the information back to the profession. The Committee had no responsibility for medicines already on the market prior to 1964 unless the Subcommittee on Adverse Reactions reported that an unexpected number of severe reactions was arising from one of them.

A committee with freedom of action, relatively untrammelled by legal niceties, can often conduct business more expeditiously than official organizations since there is a minimum of paper work, and it can make its own case-law according to circumstances and common sense. Thus, much of the Committee's contact with the applicants (the requests for amplification or clarification) took place in robust but usually good-humoured encounters over the telephone or during informal meetings, rather than in official communications duplicated for the record. Manufacturers seemed to appreciate this informal, elastic approach which perhaps did something to ease the introduction of the statutory controls which ensued. It seldom took more than four months after an application had been filed for a new medicine to be passed for clinical trial or marketing, and new formulations of standard remedies were usually dealt with in a few weeks.

Rejections were relatively few and constituted a comparatively minor part of the Committee's function: out of 3,360 submissions received between 1 January 1964 and 1 January 1968 (about 300 new medicines with submissions sometimes running into thousands of pages), only 94 were rejected though 324 were not proceeded with by the manufacturers, possibly because they were unable to produce the evidence required and retired from the contest. More important than the rejection of new medicines was the persuasion of manufacturers to alter their intentions, to modify their promotional claims, or to issue warnings to doctors when the Register of Adverse Reactions suggested that a medicine

was developing undue or unexpected toxic effects. In addition, the mere existence of the Committee may have tightened up standards. As far as possible it attempted to solve its problems by voluntary compliance and mutual agreement and this seemed to work fairly well. It might, therefore, be asked why the Government sought to effect through legislation what was being accomplished reasonably satisfactorily through the Committee's voluntary arrangements with the pharmaceutical industry. There were, however, many reasons for the new legislation which encompasses far more than the limited functions of the Committee.

Probably the least important of these reasons was to give the Committee legal power, the lack of which had not proved a serious embarrassment. There was, however, as we have seen, a great need to consolidate and simplify the somewhat chaotic legislation on medicines which had developed over the last hundred years. Further, there was also a need to provide an inspecting and licensing system to ensure the best conditions for the manufacture, storage, and distribution of medicines. For instance, there had previously been nothing to prevent a small business being set up in a back street, the products of which might not conform to the specifications filed with the applications or be free from hazards which might have been detected by a more competent staff. Then there had been remarkably little effective machinery for the enforcement of the quality control of preparations, often coming from abroad, purporting to comply with British Pharmacopoeial specifications. It was necessary also that the licence of a medicine should not only involve its proper manufacture and safety but adequate standards for its advertisement and promotion. Lastly, not only medicines for humans had to be considered but veterinary ones as well and medicated animal feeding stuffs.

The Medicines Act passed through Parliament in 1968 but only became operative towards the end of 1971 (66). In it the Secretary of State for Health and Social Services and the Minister of Agriculture who are responsible to Parliament are required to act as a Licensing Authority to issue licences governing the marketing,

importation, and manufacture of medicines for human and veterinary use. The Authority is advised by the renamed statutory Safety of Medicines Committee. It now has legal power but has very similar functions to the preceding Safety of Drugs Committee and a somewhat similar membership. It may, therefore, continue to maintain the flexibility and exercise of professional responsibility which the experience of the unofficial committee had shown to be desirable. A similar Committee on Veterinary Products advises the Authority on veterinary medicines and medicated animal feeding stuffs.

The Act also established a Medicines Commission (which is not the Licensing Authority as is sometimes erroneously thought) to be an advisory body to the Ministers on the broad aspects of policy regarding medicines and to direct the preparation of the British *Pharmacopoeia,* hitherto the responsibility of the General Medical Council. The Commission is also required to advise ministers on the numbers, functions, and personnel of the expert committees to give advice to the Authority. Except for the Pharmacopoeia Commission, such committees once established are not subject to the Commission's control, for the latter will act as an Appeal Tribunal against an adverse decision of the Authority taken on the advice of one of the safety committees. The Commission's recommendations on appeal will doubtless establish precedents to which the expert committees will probably take heed subsequently. Thus, the Act envisages the Commission not as the ordinary direct source of advice on licence applications but as a body with wide advisory functions in relation to general policy, and as an appeals court in licensing disputes about considerations of safety, efficacy, and quality. The fourteen members of the Commission consist of the chairman, four other medical men, two veterinarians, an expert on animal nutrition, two pharmacists, a chemist, two members of the pharmaceutical industry, and a stipendiary magistrate.

The Act involves the licensing of manufacturers, wholesalers, and persons responsible for the composition of medicines or their importers. Licences of Right refer to products already on the market prior to the commencement of the licensing system which do not as yet require appraisal for safety and quality. Questions of

price or comparative efficacy are excluded by the Act as considerations for refusing a licence. It is envisaged that a second stage of the Act will be implemented in the future which will involve a review of the Licences of Right, a possible control by other expert committees of medical and veterinary devices and the initiation of official compendia and publications, other than the British *Pharmacopoeia,* to give sound information on medicines to the professions.

The Act provides for an inspecting system to try to ensure the best conditions for the manufacture, storage, and distribution of medicines. The DHSS's inspectors are well-qualified men with a good knowledge of medicines, analytical procedures, specifications, production processes, and so on. There is no reason why the relationship developing between industry and such men should not be satisfactory or that constructive objective discussion with them should not be stimulating and valuable. Nor is there any reason why an atmosphere of 'we against them' should develop. The most important guarantee of satisfactory production is for inspectors to see that sound manufacturing practices and control systems exist rather than in sampling and spot-checking. The intention is (and one must remember that the road to hell is sometimes paved with good intentions) that the inspecting system should merely constitute an additional external quality control supplementary to the self-inspecting internal quality control of the firm. The tendency should be for inspectors to infuse the best procedures called from their experience gained from visits around industry and so gradually to upgrade the quality and safety of operations in the less satisfactory firms. This will result in fewer firms being able to compete with 'cut-price drugs' and will benefit the serious manufacturers as well as protect the public.

The Act also provides that all medicines must be sold from pharmacies except for simple, relatively innocuous home remedies such as laxatives, cough mixtures, and mild analgesics which appear on a General Sales List drawn up by the Commission. The list also includes an extraordinary collection of folk remedies for which we must assume there is still a market. The Commission's criterion for including a medicine in the General Sales List was reasonable safety, not efficacy or quality. There are some restrictions on the amount of mild analgesics, like aspirin, to be included

in the pack, and vitamin D is restricted in its strength as an excess can be as harmful as too little. Another list enumerates those medicines obtainable by prescription only. Here the Commission's criteria are toxicity, and the danger of producing dependence and hazard to the community. This has reduced the number of substances that could lawfully be sold by pharmacies without a prescription, but some compensation has been made to the pharmacist by allowing him to supply certain medicines without prescription (insulin for instance) to people urgently in need of them but only in amounts sufficient for three days. On the whole, in these matters, the Commission seems to have adopted a reasonable attitude regarding the individual's safety and convenience. Certainly doctors would be overwhelmed if people had to get a prescription from them every time they needed an aspirin or a laxative. When new medicines are licensed, the Safety Committee responsible will specify the classification to which they belong.

Lastly, the Act requires that any promotional literature must be consistent with the terms of a data sheet approved by the appropriate safety committee and which must accompany the product licence. This sheet describes concisely the essential facts about the new medicine in a standardized way: its generic and brand names, its dosage, its method of administration, its indications and contra-indications, and its main adverse effects. This should give the safety committee considerable powers to ensure that the indications, contra-indications, and possible adverse effects are plainly and concisely brought to the prescriber's notice. Indeed it may prevent altogether the sale of worthless remedies which the Safety of Drugs Committee had to permit provided they were safe; for if no claims are allowed on the licensing data sheet and, therefore, not on the promotional literature it will hardly be worthwhile for the manufacturer to put such a product on the market.

We have seen that the misuse of drugs, particularly by young persons and even schoolchildren, has vastly increased in the last fifteen years (p. 69). The Dangerous Drugs Acts which had been so successful in Britain proved inadequate to cope with the modern

demands for and changed attitudes towards drugs. The Drugs (Prevention of Misuse) Act 1964 attempted to bring amphetamines and LSD under a greater degree of control; but addiction to potent narcotics, particularly heroin, continued to increase and the need for new legislation to control the prescribing of drugs to addicts became apparent. Thus, the Misuse of Drugs Act (1971) came into being. Its aims are: (*a*) to control misuse of drugs of all kinds; (*b*) to categorize drugs of dependence according to their degree of danger and to grade penalties for their misuse; (*c*) to control the import, export, production, and distribution of drugs of dependence; (*d*) to regulate their prescribing and supply; (*e*) to distinguish between the offences of unlawful possession of drugs of dependence and trafficking in them; (*f*) to encourage education and research relating to drug dependence; (*g*) to continue the notification of addicts and the restriction of drugs of dependence for them and to provide centres for their treatment.

The Act is a complex piece of legislation providing a wide range of flexible controls and penalties for those who transgress the law. It would take too long to detail its provisions here but an exposition of it in comprehensible language has been given by Dr S. Bradshaw whose booklet should be consulted by those seeking further information (67).

9

Controls in other countries: the FDA; certain comparisons

The statement that medicine is international and knows no frontiers has become almost a platitude but is subject to many qualifications (68). It is true, of course, that throughout the world the medical profession has roughly the same ideals and speaks to some extent the same clinical and scientific *lingua franca*. The diagnosis and treatment of many diseases, too, such as appendicitis, pneumonia, and rheumatism are similar in different countries and therapeutic success depends on the skill of the physician or surgeon and the resistance of the patient. Nevertheless, the advent of more rapid communications and the tendency to form wider groupings like the Common Market has made it clear that it is a gross over-simplification to assume that the practice of medicine is at all homogeneous even in the western world. There is, however, a universal search for higher standards and there are great advantages in putting our long-established national conventions, institutions, and attitudes to criticism by our colleagues in other countries.

The multitude of controls imposed on the pharmaceutical industry varies enormously in different countries and even within the Common Market there are many regulations preventing the free movement of medicines from one country to another. Thus, pharmaceutical products manufactured in Britain or France can be imported freely into Germany, Switzerland, and Scandinavia provided they conform to certain specifications, but not into Belgium where all products must be packed under the supervision of a Belgian pharmacist. Although there is close co-operation in the Benelux countries it is easier for Holland to import medicines packed in Belgium than for Dutch medicines to be imported into Belgium. France has such stringent rules as to make it virtually impossible to import medicines into France at all except on a small

scale by a government agency. It is extremely difficult to find a colouring agent which will be generally acceptable on the continent, in the USA, and the UK, and there are wide variations in different countries as to the availability or otherwise of cyclamates. These are only a very few examples of the differences that operate.

Such discrepancies are not surprising when consideration is given to the rapidly changing conditions which exist and the variety of circumstances under which legislation on medicines has had to be enacted in different parts of the world. In consequence, international pharmaceutical companies encounter many frustrations and difficulties as they try to plan their production and marketing policies to conform to the widely diverse national controls that exist, some of which would seem to be unduly oppressive. It would be most desirable if broad general rules could be framed for good practices in the manufacture and quality control of medicines which would be acceptable for reciprocal agreements between nations and made eventually the basis for international legislation.

The signing in October 1971 of EFTA's Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmacological Products constituted a small advance in this connection. Though the standards were not uniform in the EFTA countries they were sufficiently similar to render them mutually acceptable and to obviate the need for authorities in importing countries to make their own inspections. The nine EEC countries have now agreed to set up a consultative committee for pharmaceuticals, running in parallel with the existing national regulatory systems, thereby giving producers the ability to cross-check the controls applied to their products in different countries. In the course of time the nine will pledge themselves either to merge their national systems into a common one or to agree on rules for the recognition of each other's regulatory controls. There is reason to believe that during the next ten to twenty years there will be a free circulation of high standard medicines with a general uniformity of quality control between the various countries. The world is contracting; no nation can now be self sufficient; everywhere ideas are crossing national boundaries with the sort of

freedom that used only to be associated with artistic or pure scientific communications.

The Food and Drug Administration of the USA is the premier drug regulatory organization in the world and has done much to protect the public; and not only the public of the USA (31*d*). For its immense task of inspecting and licensing throughout the USA the manufacture of foods, cosmetics, and pesticides, as well as human and veterinary medicines, the FDA employs at its headquarters in Washington and eighteen district offices a very large secretarial and professional staff of civil servants.

The early days of American medicine were characterized by an overstatement of therapeutic claims expressed in exaggerated advertising to the public. As a result Congress passed the Pure Food and Drugs Act of 1906, the first major American drug legislation (69). This Act was primarily concerned with the prevention of the misbranding and adulteration of products, while the subsequent 1938 Food, Drug, and Cosmetic Act provided the first governmental power in the world to rule upon the safety of medicines, preceding in this respect the voluntary Safety of Drugs Committee in Britain by a quarter of a century (70). These years saw the explosion in modern medicinal therapy and the very rapid development and expansion of the pharmaceutical industry. It is unnecessary again to emphasize the benefits thereby conferred on humanity. Nevertheless, during this period of industry's remarkable growth it sometimes became carried away by its success: without question it resorted from time to time to salesmanship rather than to a concern with what was best for the patient and the practice of medicine; it would be idle to pretend that commercial motives never prompted the sale of a medicine before its adequate investigation had been undertaken or that research workers in the industry were never under commercial pressure. On the other hand it would be equally idle to pretend that academic research workers never get carried away by their enthusiasm or that the medical or any other profession have all their actions invariably dictated by motives of pure altruism.

In 1961 Senator Kefauver (51*f*) inaugurated the celebrated congressional hearings on the pharmaceutical industry, either because of his genuine alarm at its actions or because he recognized the political profit to be gained from berating anything so prosperous, or from a mixture of both motives. During the widely publicized hearings the industry's great accomplishments were downgraded and its undoubted shortcomings and occasional scandals held up to obloquy and abuse. In consequence substantial amendments were made to the 1938 Act, imposing far greater responsibilities on the FDA. It has now to license new medicines not only for their safety but also for their efficacy. Further, the Amendments called for a retrospective evaluation of all medicines marketed from 1938 onwards. For this colossal task the FDA enlisted the help of academic experts from the National Academy of Sciences' National Research Council, and for the guidance of the panels medicines were given rating classifications of 'effective, probably effective, possibly effective and ineffective'. Lastly, the advertising provisions of the Amendments were designed to ensure that promotional literature told the truth, the whole truth and nothing but the truth.

Though science does not always lend itself to legislative or regulatory manipulation there can be little dissent that some governmental regulation of medicines is desirable: the question is the degree of such regulatory requirements; inadequate regulation may prejudice the public safety, but excessive regulation can also be prejudicial. The thoughtful legislator must direct his efforts somewhere between these two extremes: to protect the public from inadequately tested and dangerous medicines but at the same time to allow an orderly progress of research, development, and marketing by the pharmaceutical industry. The operations of controls must be efficient, economical, and rapid, for otherwise the public are denied new and useful drugs. Finally, labelling prescribed by a government agency must possess a suitable flexibility to permit the physician to exercise his judgement in the use of the drug. Very restrictive or directive types of labelling are not in the public interest.

Since the Kefauver–Harris amendments of 1962 the FDA has often been criticized, especially by the pharmaceutical industry and by many doctors, as being too restrictive in the exercise of their powers. The agency has a very difficult and often thankless task for it has to administer the law as laid down by Congress and is continuously subjected to severe political pressure to ensure the inflexible enforcement of the Congressional regulations.

Perhaps it is unfair to contrast regulatory systems in a vast country like the USA and a small one like Britain with its more homogeneous population (71). Controls are easier in the UK than in the USA as most of the leading physicians, pharmacists, veterinarians, and pharmaceutical industrialists are familiar with each other and sometimes on friendly terms, and the political atmosphere and competitive commercial pressures are perhaps less fierce. It is, nevertheless, important that we should be familiar with the workings of the FDA and make some attempt to compare and contrast it with our own method of regulation for we must confess that since the USA became far the most powerful nation in the western world we should be on our guard lest her mistakes become our actions tomorrow. Further, in the last decade there has been considerable internationalization of medicinal controls so that a governmental decision in one country (perhaps particularly in the USA) is apt to be repeated in others. Much of this is good; what has to be assured is that national prejudices will not be substituted for scientific accuracy.

In Britain ultimate power to license medicines rests as we have seen (p. 73) with the Licensing Authority (the ministers responsible to Parliament) acting on professional advice and subject to appeal to the Medicines Commission on which the pharmaceutical industry is represented. The decisions of the committees advising the Authority are taken by part-time, virtually honorary, professional men whose careers in no way depend on their membership of the committees on which they serve largely as an altruistic public chore. They are assisted by a small staff of expert professional civil servants who do most of the work but the decisions are not taken by them.

In the USA on the other hand, ultimate power rests with the full-time professional civil servants of the FDA whose careers do

depend very much on the correctness of their decisions which are subject to formidable grillings by congressional committees.

An official charged with approving or disapproving a new medicine can make two kinds of mistake: (*a*) he can approve a medicine that turns out to have unanticipated serious adverse effects; or (*b*) he can refuse approval of a medicine that could have been life-saving with few toxic reactions. If he makes the first mistake his folly will be emblazoned in the public media and he will be disgraced; if he makes the second few will know of it and the people whose lives might have been saved may not be there to protest. It is thus only natural that there should be a disinclination to give approval to a potentially good medicine in order to avoid the possibility of approving one that will have unexpected adverse effects. It may be that in their hesitation to approve a medicine the FDA do sometimes set a barrier to bona-fide research and progress because there is always a tendency to think up yet another test on a new medicine to avoid the necessity of coming to a decision. Time and again pharmaceutical companies in the USA complain of being forced to undertake unnecessary and costly tests in time and money to justify further delay before a decision is made. Redress against a decision of the FDA can only be sought in the law courts, involving considerable expense and the law's interminable delays.

The fairly rigid rules imposed by Congress under which the FDA has to work often seem to rely excessively on somewhat artificial animal experiments though it is very difficult to extrapolate observations on animals to man: for example, their decisions in recent years on cyclamates, hexachlorophene, and practolol. The decision to ban cyclamates was necessary because of the Delaney Clause in the Amendments which makes it illegal to include substances in food found to induce cancer in any animal species. If recent reports are true it may well be that saccharin itself may be in danger in the USA. In the USA the regulatory response to the finding of practolol's carcinogenicity in mice has been to require further carcinogenicity tests of the newer Beta-adrenergic-blocking drugs in animals. However, the number of humans in other countries who have received or are currently receiving such drugs is already many times greater than the

number of animals normally required for such toxicity tests. The money would have been much better spent in the scientific surveillance of patients in other countries who have received or are receiving these drugs. It is doubtful if rigid laws can suitably be applied to the licensing of medicines since each one presents an individual problem to be treated with common sense.

It takes very much longer for a new medicine to be licensed in the USA than it does in the UK and involves great expense. There are those who say that the history of the handling of thalidomide in the USA is a classic example of the great rewards of uninformed procrastination though this may well be grossly unfair to the perception of Miss Kelsey who was for this matter awarded a Presidential Citation and congressional gold medal. Dr Joseph Sadusk (72) the Vice-President for Medical and Scientific Affairs of Parke, Davis and Company and at one time an official of the FDA, states that it is now generally agreed in the USA that it takes about eight years on the average to bring a new medicine to the market from the time of its chemical synthesis; and Harold Clymer, Vice-President for Research and Development of Smith Kline and French, estimated a period of anything from four to nine years. It is difficult to obtain accurate data regarding the impact of drug regulation upon the cost of bringing a new single entity medicine to the market in the United States, but their Pharmaceutical Manufacturers Association have estimated an average figure of about $6 million. For example, the documents recently submitted to the FDA requesting permission to introduce a new drug to treat Parkinson's disease consisted of 504 monographs, each 4·8 cm thick. The total thickness of the dossier was 24 metres! We must not, however, be complacent about our regulatory system in this country for though over all it takes a much shorter time to license a medicine here than in the USA and involves less expense, yet at the present time it takes longer to get permission for a new medicine to be put to clinical trial in the UK than in any other country in the world.

The increasingly stringent regulations, the expense and the delay involved in the introduction and marketing of medicines have made firms in the USA more chary of developing new products, especially those exhibiting only marginal advantages

over existing preparations (73). In the last decade the number of new drug applications to the FDA have fallen from about 260 a year to a little over 100. Unless incentives are very strong, investigators are apt to abandon the development of a medicine in its early stages if some unexplained side-effect is encountered. It is sometimes stated that under present requirements aspirin would never be approved by the FDA. This may be nonsense, but it might well be that under present circumstances a company would be unwilling to undertake and complete the development of aspirin, knowing the difficulties in demonstrating its efficacy and that it has significant and occasionally serious adverse effects. As has been pointed out (p. 17) the reduction in the vast number of new remedies which have flooded on the market, differing only slightly from each other, has had advantages as well as disadvantages.

A major consequence of the Kefauver–Harris amendments is that new medicines often tend to be released in Britain a long time before they become available in the USA, and there are at present a number of medicines which we consider to be of significant therapeutic value which are as yet unavailable there. It would take too long to discuss these in detail in this monograph: the whole subject has recently been carefully reviewed by Wardell (74). The important question to answer is whether the benefit of the high margin of safety imposed by the stringent FDA regulations is outweighed by the harm done from delay in introducing or in postponing altogether the use of valuable new remedies. For example, how many hundreds of thousands of persons would have died from pneumococcal pneumonia if it had taken some eight years to license sulphapyridine (M & B 693)? Professor Peltzman (75) in a brilliant, if somewhat complex and lengthy paper presented at a recent conference at the University of Chicago in which he has explored these questions in detail, has no doubt as to the answer: the harm done by delay has greatly outweighed the good.

During the last ten years the control exercised by the FDA on package inserts and pharmaceutical advertisements has resulted in a greater accuracy and veracity in the advertising of medicines in the USA than that existing in Britain where such promotion is

still sometimes subject to justifiable criticism (p. 51). We have seen, however, that under the Medicines Act (p. 76) the data sheets which must accompany all product licences and to which all subsequent promotional literature must adhere will go far to remedy this and to prevent totally unwarrantable claims. These concise data sheets will be very different from the elaborate disclosures insisted on by the FDA in package inserts which are very detailed and a little apt to read like horror stories, for every possible adverse reaction must be included. Further, the approved uses of a medicine in the USA, say, like propranolol, are restricted in the package inserts to cardiac arrhythmias of specific types, phaeochromocytomata, and hypertrophic subaortic stenosis. Angina pectoris and hypertension are not approved uses for propranolol in the package inserts and yet these have been well documented in both the British and American literature. There seems to be no reason why the prejudices of an official in the FDA or of his advisors should predominate over even a minority of responsible medical opinion by excluding these latter indications. Doctors in the USA are subject to civil actions by patients for malpractice far more often than in the UK and such actions are much more frequently successful. In consequence they are becoming chary of deviating in their practice from the indications in the package inserts of the FDA which are thus having the effect if not the actuality of regulations.

In the UK the Licensing Authority does not deny a minority the right to use any medicine it desires provided it is reasonably safe for its intended purpose. Herbal and homeopathic remedies are examples of the principle involved. Of course, the pronouncements of the FDA in package inserts are only guidelines and not official directions, just as in Britain there are guidelines in therapeutic publications.

The Medicines Act in Britain forbids the comparative efficacy of medicines to be taken into account in their licensing. The primary concern of the Authority in the UK is to try to ensure the safety and quality of medicines for the purposes for which they are to be used rather than to act as an arbiter of therapy regarding their efficacy *per se*. It is believed that opinion on matters of efficacy should not be formed so much by bureaucratic bodies

as through the free processes of scientific publication, debate, and undergraduate and postgraduate education; that there should be no chance for prejudiced individuals to impose their ideas on the medical profession and community; and that there is no safe depository of ultimate power in this matter save the medical profession. If the latter be thought insufficiently enlightened to exercise that power with a wholesome discretion the remedy is not to take the power away from it but to improve its discretion by education, particularly in the hitherto somewhat neglected subject of clinical pharmacology (p. 34).

In the USA on the other hand it is thought to be completely irrational to attempt to distinguish the safety from the efficacy of medicines for no medicine is safe which fails to cure a disorder for which a cure is available (76). Thus, it is the duty of the FDA to try to prevent the needless suffering, protraction of illness, and the squandering of public money on ineffective and unnecessary medicines. Most doctors see insufficient patients suffering from any one disease to evaluate critically the medicines employed for it and can only gather impressions about the ones they use. All doctors are not equally knowledgeable about all medicines and it would be absurd to expect them to be so. It is, therefore, the duty of the FDA to assist doctors by strict supervision of the efficacy as well as the safety of old and new remedies; and whether a medicine is sufficiently safe and efficacious to be marketed must be decided by the FDA helped by panels of experts from the National Academy of Sciences' Research Council who are less likely to be wrong than non-experts.

Today the FDA is implementing the recommendations of this study which might well be taken to represent the best judgement of the scientific community. Nevertheless, there is evidence of increasing doubt, in which Dr Louis Lasagna shares (himself a chairman of one of the panels) whether the current regulatory policy is in the public interest (77). To begin with the study was necessarily imperfect. The magnitude of the task, some 3,000 medicines and 10,000 claims precluded attention to detail or the presentation of extensive supporting information from the manufacturers. The rating classifications of 'effective, probably effective, possibly effective' were not clearly defined or easy to

apply and were often interpreted very differently by the various panels.

A second major source of confusion arose from the agency's inconsistent approach to older remedies. It has been understood in the case of some well-tried medicines which had years of clinical experience to support their claims that they would be accepted although they might never have been subjected to the controlled trials demanded of new medicines. Then, the early pronouncements by government officials indicated that the evidence for the efficacy of a new drug must be 'substantial' rather than 'preponderant', so that a respectable minority opinion on efficacy could justify its approval. More recent FDA regulations have defined 'substantial' evidence so narrowly as virtually to exclude minority opinions. Lastly, the history of the Kefauver–Harris amendments makes it clear that Congress originally intended to avoid, as in this country, judgements of comparative efficacy. There was no intention to prohibit the sale of a medicine because it was thought to be a little less effective than another used for the same purpose. Yet many recent examples can be quoted involving judgements based on comparative efficacy.

A former well-known Commissioner of the FDA poured scorn on the suggestion that a gradual process of medical education might in the long run produce sounder results than the more immediate effect of legal edicts. He said in so many words that when the house is on fire an academic lecture on how to control incendiarism is inopportune. What is needed is to put out the fire and only when that has been accomplished is it appropriate to give lessons on how to prevent further fires in the future. It is somewhat surprising that in the USA, the home of big business and free enterprise, the control of medicines should be far more bureaucratically rigid than in this country with our so-called socialized medicine. It is possible, however, now that our regulation of medicines has come so much more under the law, that our agencies will more and more arrogate to themselves the duty of dogmatizing on the efficacy of medicines. Thus there is a danger that a so-called learned profession might eventually be reduced to signing forms entitling their patients to receive such medicines

for such purposes as the regulatory agencies permit. It would be a pity if in our efforts to improve the public's physical health by our control of medicines we fell into the same errors which long ago afflicted the Inquisition in their efforts to control the public's spiritual health.

10

Future prospects

It is usual to conclude these monographs with a little speculative crystal gazing. Many of the most mentally agile people are so intensely inquisitive about the immediate future that the prospect of dying before they find out what is going to happen is abhorrent to them. Less intellectually active and curious individuals, especially perhaps if they have led happy lives, become in the evening of their days nostalgic about the past and find the contemplation of the brave new world and speculation as to its future faintly distasteful. In their old age the latter do not therefore view the prospect of dissolution with any apprehension, and would in fact be glad to call it a day if only they could 'cease upon the midnight with no pain'. It is the contemplation of the process of dying, the gradual physical disablement, the discomforts, and the mental deterioration, which is so disagreeable.

In the absence of some atomic disaster or other unforeseen fatal pollution of the environment, the average expectation of life will almost certainly increase still further during the rest of this century due to therapeutic advances. This will result in an ever-growing number of old people suffering from various forms of physical deterioration and depersonalization which will inevitably increase the already existing demand for the legalization of euthanasia by drugs. The advantages of euthanasia must surely be outweighed by the complex ethical and legal problems and even the abuses which it would certainly engender. As wise old Lord Melbourne said of euthanasia to his young Queen: 'If they get the habit of doing such a thing when a person is in a hopeless state, why, they may do it when a person is not in a hopeless state.'

It would surely be most undesirable for doctors to abandon in this respect their Hippocratic oath and to arrogate to themselves such a Jehovah-like responsibility. They have now plenty of such responsibilities without adding to them. They are already involved in far greater ethical decisions than ever confronted

their predecessors earlier in the century: the ethics of organ transplantation, involving the accurate diagnosis of death (the exact moment when the soul is supposed to have broken cover from its temple); the best way to control the population explosion; the correct answer to abortion on demand; the degree to which the medical profession should communicate with the public in the press and on television; and how long to preserve life by antibiotics, respirators, and so forth when the need for it seems to be passed. The negative avoidance of needlessly striving to keep alive is quite different from the positive destruction of life.

It would be an act of supererogation in this monograph to attempt a Delphic forecasting of advances in the therapeutic practice of medicine during the remainder of the century, for this has already been undertaken by a brilliant team of experts organized by the Office of Health Economics, *Medicines in the 1990s*, and the following is largely a repetitive short summary of some of the more apposite of their forecasts (78).

If the last quarter of a century will be particularly remembered in therapeutic history for the introduction of antibiotics, corticosteroids, hypotensives, anticoagulants, and thiazide diuretics, the next twenty-five years will probably be famous: (*a*) for progress against virus infections by an extension of vaccine therapy and the elaboration of antiviral compounds; (*b*) for the introduction into practical medicine of the prostaglandins with their extraordinary variety of pharmacological and potentially therapeutic actions; (*c*) for the ability to suppress more effectually harmful immune responses, which is so necessary for the solution of the difficulties of transplant surgery, the treatment of rheumatoid arthritis and so forth; (*d*) for the prophylaxis of coronary heart disease, peripheral vascular disease, and strokes by medicines with the ability to control the laying down of fats in the walls of arteries, and to effect the formation of thrombi perhaps through their action on platelets and fibrinogen; (*e*) for more effective medicinal treatment of mental illness based on the advance in our knowledge of the biochemistry of personality disorders and a greater rather than less use of medicines for the control of mood as suggested years

ago by the cartoon in the *New Yorker* magazine which depicted a young woman saying: 'I don't know whether to take a Benzedrene and go to the party or a Seconal and go to bed!'

It is interesting to speculate on the future relationship of the pharmaceutical industry to governments. It is at least fairly safe to conclude that by the end of the century social security schemes of one kind or another, providing medical care for everyone, will be universal in civilized countries when in consequence the state will everywhere have become the chief customer of the industry. Under such circumstances a clash of interests is only too likely to occur. On the one hand powerful international companies with plenty of political influence may seek to free themselves from what they believe to be shackling controls, inhibiting their profits by undue price regulation and hence their expansion, research, and innovation; and on the other governments, often increasingly left wing in outlook, and yielding to sometimes irrational public and medical demands to ensure the safety of medicines and to limit the undue profits of industry, may seek to impose increasingly rigid standards upon the price, introduction, and promotion of medicines by the industry. Some governments might well attempt to establish through a national state-owned industry an alternative source for the production of medicines as has already occurred to a very limited extent in Sweden and more particularly in India.

All this would be most unfortunate. The whole success of the future of therapeutics depends on the close co-operation of industry, government, and the medical profession, each of which together have so much to contribute provided their efforts are harmonized. In a very small way this harmonization was perhaps demonstrated to be a practical proposition in the time of the voluntary Safety of Drugs Committee.

Industry must make sure that its profits are 'not unreasonable', that inaccurate, excessive, and vulgar promotion of its products is avoided and that its altruism matches its commercialism. Government must avoid irrational requirements for the safety of

medicines especially when undertaken as the result of hysterical pressures by politicians, consumer groups, and the public media. Safety regulations by over-emphasis may be counter productive by inhibiting rather than encouraging experimentation leading to further knowledge about medicines. Such regulations must take into account the benefit/risk ratio in realistic terms. The medical, dental, and veterinary professions must show a greater responsibility, knowledge, and wisdom in the use of the formidable agents which have been put into their hands, and realize that continuing instruction in their use is essential. They must accept the responsibility of sustaining their own freedoms by keeping their own house in order and not providing ammunition for their carping critics. 'The price of freedom is eternal vigilance.' Finally, more account should be taken of the results of pharmacological and clinical trials of medicines in other countries, thereby saving time, money, and manpower in duplicative work and paving the way to an international system of regulation incorporating the best in existing national schemes.

Lastly, just as not every qualified doctor is expected to be competent to undertake a subtotal gastrectomy or thyroidectomy so some limitations should be imposed on those permitted to use certain medicines. Yet, all existing regulatory agencies start with the assumption that all doctors are equally competent in this respect. This is not the case for very specific skills are sometimes required to administer very specific medicines. Further, very potent new medicines could often be marketed much earlier with great benefit if their use was to begin with limited to experts before massive general prescribing was permitted. This is exactly what happened when limited quantities of cortisone first became available in this country and by the time it was generally prescribable its indications and contra-indications were fully understood. The matter is well summarized by Professor Lasagna and represents a reasonable approach to the problem of the control of medicines. A quotation from his lecture appropriately concludes this monograph:

You need only a relatively small amount of good clinical work to establish that a drug is effective and reasonably safe. It takes a lot of work, however, to pinpoint safety and efficiency with precision. It takes years to find out all the potential toxic mischief that drugs have. One might argue that you could introduce new drugs, therefore, rather early on the market if you could feel assured that there would be some sort of gradual use of the drug as opposed to massive prescribing by every doctor in the country to every patient. What you would like to have is gradual introduction and efficient monitoring of the safety and efficacy aspects of that new drug so as to revise as frequently as necessary the indications and contraindications for the drug. Also, you would like to have an effective means of communicating this to doctors. All of these aspects are tied together. If you believe, as I do, that it is possible to get a pretty good feeling for a drug relatively early in the game, then it seems wasteful to spend years getting more data just so that people can have a spurious sense of confidence in what they know and do not know about a drug.

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