OHE 20th ANNIVERSARY SYMPOSIUM

THE SECOND PHARMACOLOGICAL REVOLUTION

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Edited by Nicholas Wells

THE SECOND PHARMACOLOGICAL REVOLUTION

A symposium
held at the Royal College of Physicians,
London in September 1982 by the
Office of Health Economics
to mark the 20th Anniversary
of OHE

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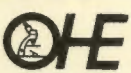

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Contents

Foreword

The Rt Hon Norman Fowler MP
Secretary of State for Social Services

I take great pleasure in contributing this foreword to the published proceedings of the symposium on the Second Pharmacological Revolution.

I would like to pay tribute to the work of the Office of Health Economics over the past 20 years, as celebrated by this anniversary symposium. The OHE has recently been described in the press as the 'research arm of the British pharmaceutical industry' and a 'think tank'. Such descriptions testify to the standing of the OHE and to the success of its Director, Professor George Teeling Smith. During these 20 years, its impressive record includes no less than 73 surveys in its Studies of Current Health Problems series and an equally impressive number of briefings, reports and monographs. I congratulate the OHE on their immensely valuable work.

A look backwards also cannot help but encompass the impressive list of British achievements in discovering new and better drugs. The discovery of the first antibiotic – penicillin – was followed by the semi-synthetic penicillins, the cephalosporins and co-trimoxazole. Salbutamol, sodium cromoglycate and inhaled beclomethasone dipropionate have revolutionised the treatment of asthma. Ibuprofen was a seminal advance in the treatment of arthritis and allopurinol marked an important advance for sufferers from gout. Cimetidine and (more recently) ranitidine have had a profound effect in the treatment of duodenal ulceration; and of course many patients have benefited from propranolol and other beta-blockers. These and other achievements speak eloquently of the benefits which flow from what Professor Teeling Smith has described as the tripartite relationship between the industry, the academic world and Government.

The Government role has been, and will continue to be, to foster a relationship which encourages the industry to provide a continuing flow of better and safer medicines for use in the National Health Service and which at the same time enables the industry to sustain its vigorous and successful research and development programme on which the promise of the second pharmacological revolution and the future success of the industry in the UK so heavily depend. Success is of course shared by British and foreign firms alike. It gives me pleasure to acknowledge the contribution which they have made to advancing science and technology, to employment and particularly to the UK balance of trade. With a contribution of £570 million in 1981, the pharmaceutical industry was second only to manufacturers of machinery as a net exporter from Britain.

I join with the various contributors to the symposium in wishing the industry and the OHE continuing success.

Introduction

Nicholas Wells
Office of Health Economics

The thesis underlying the symposium recorded in this volume is that pharmacological and biomedical understanding have now advanced to a stage such that it would appear feasible to anticipate a new era of therapeutic progress. It is postulated that effective medicines will become available for a range of hitherto untreatable or inadequately controlled diseases and that, in broad terms, their principal distinguishing feature will be the fact that they have evolved as a consequence of enhanced knowledge of intracellular chemistry. By contrast, the development of the anti-infective drugs, which formed the backbone of the First Pharmacological Revolution, reflected discoveries at the intercellular level. The differentiation of pharmacological advance into specific epochs in this manner raises a plethora of complex issues but three in particular merit detailed consideration. First, is the basic hypothesis tenable? Second, if this is the case, can the efforts required to harness the potential achievements be justified? Finally, given affirmative responses to both these questions, what obstacles might serve to limit the desired rate and extent of progress?

Addressing the first of these points requires speculation about the nature of potential developments and an assessment of whether or not the latter constitute a sufficiently marked departure from existing therapeutic possibilities to warrant classification as part of a Second Pharmacological Revolution. It is of course axiomatic that predicting the future is a precarious exercise, not just in the context of pharmaceuticals but in every sphere of human endeavour. Thus spaceflight, modern computer capabilities and foetal surgery would have been inconceivable to all but the most prescient of preceding generations as would also have been the case with pharmacological control of tuberculosis or the reproductive cycle. Furthermore, it might be argued that, paradoxically, as the interstices in our knowledge gradually become diminished so too does our capacity for confident prediction.

In spite of these comments, the speakers assembled for the second session of the symposium were able to define a number of areas where continued research should prove therapeutically fruitful. For example, the elucidation of prostaglandin chemistry, stemming in large measure from the pioneering investigations of Vane and Bergstrom who, incidentally, shared with Samuelson in this year's Nobel Prize for Medicine for their contribution in this field, should pave the way for new treatments of the various manifestations of vascular disease. Bright prospects are also offered by research into anti-viral preparations. Of these attention has in particular been given to the interferons which might yield effective therapy for herpes simplex, varicella zoster and common respiratory infections. In the context of autoimmune disorders, there is not only hope of directly controlling certain conditions but also the possibility of employing new knowledge to identify individuals with a heightened risk of succumbing to such disease processes following, say, viral infection. Focusing on the cancers,

success has already been achieved in controlling certain types of malignancy – for example, acute lymphocytic leukaemia, Hodgkin's disease and testicular carcinoma – and continued research aimed especially at identifying the 'strategies' adopted by cancer cells to promote their own survival should lead to more tumour types becoming susceptible to chemotherapy. Concurrent with all this activity, further refinement of the techniques of genetic engineering will facilitate the production of a great variety of biologically potent polypeptides and proteins with high degrees of specificity and in quantities that are theoretically unlimited.

Inevitably, the foregoing has done little more than skim the surface of future potential pharmacological advance and many other possibilities have been described elsewhere. Nevertheless, the clear message is that our aspirations successfully to treat many of the disorders that are now significant elements in today's morbidity and mortality profiles can be realised. But whether or not this new era of progress is appropriately designated the Second Pharmacological Revolution provides an interesting point for debate.

Innovation is rarely a clearly defined process whereby advances of a particular type can be neatly parcelled up and assigned to one specific era. Instead it assumes more frequently the form of sustained evolution with progress reflecting modifications and improvements to the fruits of preceding phases of advance. Furthermore, it requires little emphasis that the identification of different stages of development is a function of the historical perspective underlying the analysis. However, the concept of a Second Pharmacological Revolution is perhaps particularly apposite in the specific context of the pharmaceutical industry's role in therapeutic advance and provides a useful frame of reference for discussing the issues at the centre of this symposium.

The second question posed at the outset of these introductory notes asks quite simply whether in fact we want to take advantage of the therapeutic promises waiting on the horizon. This question is not as unworthy of consideration as it might appear at first sight. For example, the action being either taken or considered by a number of national governments in the current economic recession to contain public expenditure on pharmaceuticals has serious implications for drug innovation. Short-term expedients such as downward pressure on real price levels or the imposition of restrictions on market access not only diminish the funds available to pharmaceutical companies for research and development (and these requirements have escalated enormously in recent times, an estimated £50 million now being needed to bring a new chemical entity from the laboratory to the status of a successful prescribable medicine) but also damage investment confidence. The consequence of the latter may not become apparent for a number of years because of the long lag times operative in pharmaceutical innovation (ten or more years in the case of a major new chemical entity) and this fact coupled with the attraction of the supposed 'savings' associated with specific strategies means that there is little immediate disincentive to what will eventually emerge as imprudent intervention. It may be the case that the industry's protagonists have yet to educate governments sufficiently about the dangers of such action. Alternatively, if the latter are in fact recognised, the advent of initiatives of the

type described above could be interpreted as an implicit questioning of the need for new drug development.

The same point might also be inferred from an examination of contemporary mortality patterns. Thus a substantial proportion of premature death can be attributed to causes which have been shown by epidemiological investigation to be 'environmental' in nature. Consequently, it is argued that such fatalities are most appropriately prevented by suitable modification of the deleterious factors involved rather than resort to a convenient 'technological fix'. In this context, coronary heart disease provides perhaps the definitive paradigm. The disease is responsible for 38 per cent of the 73,000 male deaths occurring between 30 years and retirement age in England and Wales. The medicines currently available are only employed once disease has been diagnosed, either to alleviate symptoms or to prevent their recurrence; they neither ameliorate the underlying damage to the arteries of the myocardium nor avert further deterioration. Even if a preventive medicine were to emerge, there would be immense difficulties in constructing appropriate criteria for treatment, especially in view of the uncertainties surrounding indefinitely prolonged medication. The solution to the problem, therefore, lies in more widespread action on the well-established risk factors for the disease.

It is undeniable that arguments advanced along these lines contain much that is valid. Nevertheless, the case for sustaining the search for new medicines remains overwhelming. Although developments are unlikely to be such to imitate the impact that the drugs of the first wave of pharmacological progress had on mortality, there are still many areas, perhaps most notably the cancers, where a significant saving of life can be achieved. It seems more probable, however, that the major contribution of the Second Pharmacological Revolution will be realised in terms of reduced morbidity and disablement as opposed to diminished mortality levels. Thus arthritis, multiple sclerosis and mental disorders are examples of specific targets within an overall strategy which has as its principal objective, in the developed world at least, the addition of 'life to years rather than years to life'.

One immediate implication of this projected trend is that the 'indirect' benefits of medicines will become much more difficult to define and quantify. Previously, it was a relatively straightforward exercise to demonstrate the economic gains generated, for example, by the anti-tubercular medicines: the resultant reductions in mortality, hospital admissions and sickness absence from work were readily expressed in financial terms, revealing substantial savings over the costs of the necessary chemotherapy. In the case of medicines whose essential bearing is on the quality of life, such economic advantages are markedly less conspicuous. Instead the benefits are manifest in social or psychological gain leading to more normal functioning. The transition from first to second revolution therapeutics is, therefore, going to generate a concomitant need for more appropriate methods of representing the benefits of new drug development.

Pharmaceutical innovation also merits explicit encouragement from a broader economic perspective: a successful drug industry is a valuable asset to the economy. Thus the companies operating in Britain provide direct employment for more than 70,000 people and in 1981 contributed net

export earnings of more than £550 million to the nation's balance of payments. It may be speculated that sufficient encouragement given to drug innovation might lead to a bettering of even this highly successful record and that the industry could well emerge as one of the key facilitating sectors in the forthcoming economic recovery predicted by the Kondratieff innovative cycle theory, if by no-one else. The former is based on the work of a Russian economist of that name who discovered regular long-term (50–60 years) cyclical fluctuations in economic activity. These observations were then adapted by Schumpeter to form the basis of a theory the principal postulate of which is that bursts of innovative activity lay the foundations for subsequent periods of economic growth. Thus the discovery of smelting iron ore with coal and the mechanisation of the cotton industry facilitated the first industrial revolution. It is predicted that continued research in areas such as microprocessors and bio-engineering during the recession of the 1980s should generate innovation-led recovery during the following decade. There is, therefore, the interesting possibility that genetic engineering could be one of the foundations of both the fifth Kondratieff cycle and the second 50 year cycle of the pharmaceutical industry.

The remaining issue mooted at the start of this paper concerns the current and potential impediments to progress in pharmaceutical innovation. In this context, a recurrent theme throughout the symposium was the high cost of research and development. It is estimated that funds allocated to this activity by the British industry have risen from £29 million in 1970 to more than £330 million in 1981. Yet there has been no evidence of a corresponding upsurge in the number of new chemical entities introduced onto the market; indeed the annual figure has remained more or less constant over the last decade or so with, if anything, just a slight tendency towards a declining major innovation rate. The explanation for this trend reflects a number of factors, one of the most important of which is the disproportionately large increase that has occurred in the expenditure necessary to generate a marketable new chemical entity. The principal impact of this development has been progressively to reduce the number of companies capable of amassing sufficient funds to permit participation in the search for breakthrough drugs.

There is, of course, no straightforward panacea to this problem. One approach might be to expedite the availability of adequate levels of finance for research and development by appropriate adjustments to allowable prices and profits but, as indicated earlier, the deleterious effects of economic recession on the buoyancy of public finance would appear to inhibit the scope for action of this type in the immediately foreseeable future. An alternative strategy might seek to reduce the cost of innovation itself. This could be achieved, for example, via a reduction in the length of the development period currently endured by new medicines. At the same time this would also facilitate earlier marketing and thus the scope for recouping research costs sooner rather than later in the life cycle of any given product. The inevitable counter-argument to possible alterations along these lines involving a diminution of regulatory testing requirements draws attention to the 'avoidable' dangers that might accompany the 'premature' release of new medicines for patient use. The issues bound up in this debate are legion and complex and although they cannot be contemplated

in any further detail here, the reader will find that they are discussed at length in several of the contributions contained in this volume.

The foregoing does in fact also serve to emphasise that the obstacles confronting continued pharmaceutical innovation are not solely of an economic nature. The creation of a social environment in which the evolution of new medicines is regarded as a necessary and valuable process meriting sustained encouragement and practical support has equally to be accomplished if the potential of the Second Pharmacological Revolution is to be fully realised. In this context, priority ought perhaps to be given to the education of the public in the concept of risks and benefits as they apply to modern chemotherapy. To date, the difficulties of quantifying the benefits of many medicines (which, as suggested earlier, are likely if anything to become more problematic) and their inherently un-newsworthy nature in contrast to the in-depth media investigations usually forthcoming in the event of, say, the discovery of an unsuspected adverse drug reaction have inhibited the promotion of a widespread and balanced understanding of the issues involved. In general terms, there is, therefore, a need for a greater awareness of the special characteristics which differentiate medicines and their use from the more familiar products encountered in everyday life. However, as educative efforts in other health dimensions have made patently clear, the effective dissemination of information and the creation of realistic expectations among the general public represent tasks of formidable magnitude.

This symposium was organised by the Office of Health Economics to mark the 20th anniversary of its foundation. Yet the significance of the occasion extended beyond the straightforward celebration of two decades' endeavour. It was, in addition, a formalised recognition of the fact that society is on the brink of a new era of drug development. There are genuine prospects for significant advance in the control that can currently be exercised over disease and these will be accompanied by the economic benefits that should flow from a vigorous pharmaceutical industry as it enters the second 50 years of its history. It is unfortunate, therefore, that this phase of evolution has been attained at a time of economic recession which could threaten to stifle the necessary encouragement the innovative promises deserve. Nevertheless, the message to emerge from the papers presented to the symposium is that the obstacles to progress are increasingly being recognised and that there is a growing determination on the part of all parties to the dialogue to ensure that they do not cast a shadow over a potentially bright future.

SESSION I

SETTING THE SCENE

Chairman The Earl of Halsbury, *Brunel University*

Ladies and gentlemen, you are met to consider the second revolution in pharmacology, and you have honoured me by inviting me to give the opening address. If I am not to transgress on the very interesting list of topics which have been apportioned among the speakers, what remains to me is of such generality that I hope you will not think it irrelevant. Let me therefore ask the sort of question that concerns me at my time of life when I am reconciled to being left behind by the advancing front of knowledge, namely, could there be any feature in the world which places limits thereon, that is, limits on knowledge, suitably defined?

The whole of science from the Ionian hylozirsts onwards has been based on one metaphysical principle, that the universe is intelligible, that we can understand it. This is not a deduction from science; it is the grounds on which the possibility of science is based. I can see a cloud on the horizon of mathematical physics which might give pause for thought: the gauge theories which claim grand unification of the four fundamental forces of nature as the broken symmetries of a deeper underlying unity are verifiable only at energies so vastly in excess of our powers to attain them that they cannot occur or ever have occurred later than the first microsecond of what is called the hot big bang (if there ever was one). We would end in a state in which our beliefs about nature appeared unverifiable. Would we then feel nature to be no longer intelligible? And what would be the effect on us and our confidence in science if we had to face that situation?.

Biology and biochemistry are our business, not physics, here today, but some of the same questions can be asked. Are there intrinsic limits of knowledge in this field? We are going to think and talk about a second revolution. Will it lead on to a third and thence to a fourth, and so on indefinitely? If not, will we reach finality of a kind where we appear to know everything or of a kind where we have to accept some sort of ukase to the effect: thus far and no further?

When I was a student I accepted that so far as plants were concerned there was a protoplasmic continuity throughout the body of the plant through pores in cell walls, such that the cellular structure was merely a device ensuring some kind overall structural rigidity by local bracing. Recent techniques of freeze fracturing make it clear that animal cells have an extremely complex system of internal plumbing on the one hand and of intercommunication on the other. When I was a student the reduction of the macroscopic to an aggregate of microscopic cellular units left the mechanism whereby they co-operated as a unity, somewhat mysterious. Ought we now to think of ourselves as giant macromolecules and life as some kind of macroscopic quantum effect involving co-operative behaviour at room temperature analogous to superconductivity and the co-operative behaviour we find in liquid helium at very low temperatures? Will the mobile cell boundaries turn out to be two dimensional computer tapes

whose control programmes are stored locally? Shall we be able to understand them? Is a cell a truly three dimensional object or a crumpled up two dimensional membrane? How do we visualise the passage of a T or B lymphocyte right through one cell?

When I was a school boy studying Perkin and Kipping's textbook on Organic Chemistry I learned that Emil Fischer had synthesised an octa deca peptide, and got laughed at for my pains, such knowledge not being for boys. Today any sixth form boy can look at a model of a protein in three dimensions, but how much of it does he really take in? The study in depth of the three dimensional configuration and structure of a single protein is something which a mature chemist or biochemist can occupy himself with for many years. What chance have we of being able to assimilate the interaction of ten thousand or so of such complicated units or of understanding the programming of the control system which endows the whole with homeostasis? Is the programming of mitotic cycles repetitive without limit, or is a cell only programmed for a limited number of mitoses? Is that why they transform in tissue culture after a characteristic number of self-replications? Could it be true of species on some more extended scale? That a species is only programmed for so many meioses after which it mutates by some kind of jump command? Is the whole adventure of life on this planet preprogrammed in the first chromosome? A great part of our chromosomes appears to be blank tape. Is it waiting to be written on?

Should we turn to the computer for an evaluation of events? Do we believe things to be true because the computer says so? Is that what we call being intelligible as the grounds of a science whose application yields, inter alia, computers? The problem is already vexing number theorists. If the computer asserts that some quite enormous number, some number as to which one could never count up to in a lifetime, is the smallest number with some interesting number theoretic property, do we accept that as true? Suppose two different programmes with different computers reached the same conclusion. Are our beliefs reinforced if it is beyond our skill to verify that they agree because they have both made the same mistake, not a random mistake, of course, because that could be detected statistically, but a conceptual one? Think, for example, of how geometricians were misled for millennia because they thought the axiom of parallels was the only basis for geometry.

I cannot say whether this is where the second revolution will end up or whether it will lead to a third, which will raise its own questions on the limits imposed on what we can hope to regard as intelligible. What we can all be sure of is that the second revolution is only just beginning to make itself felt. We begin to understand the complexities of self-replication. The late Professor Waddington told me that he had listed some fourteen thinkers, of whom I had been one, all of whom had realised that self-replication must be a two-strand process. It was the unique merit of Crick and Watson that they reduced the precise mechanism and structure of the process to chemical terms. We still know very little of the control mechanism. Professor Gurden's very deep experiments make it clear that however differentiated a cell may be, it is still totipotent, as is often manifest when tumour cells secrete atypical hormones, for example, insulin or ACTH secretion by lung tumours. The astonishing versatility of the steroid

skeleton mystifies me now as much as it did when I was a student.

Are we on the verge of a transformation of clinical medicine from an art to a science by absorption of pathological conditions into a quite limited number of classificatory headings? Once upon a time crystallography consisted of people with a sense of inquisitiveness rambling around mountain torrents and streams, looking at rocks and collecting brightly coloured, shapely things. It became a science when it was classifiable into thirty-two different types of crystal symmetry. Will clinical medicine go this way?

A gene too few as in phenylketonuria or haemophilia, a chromosome too many as in mongolism, a breakdown of the control mechanism as in neoplasia, malfunction of the monitory system as in the auto-immune diseases, to which insulin dependent diabetes may be a recent recruit, infection and modification of the host by foreign genetic material, and so on, possibly a limited number of such classificatory headings for students to learn. Yet they would still have a lot to learn and so do we before we reach whatever barriers there may be to going further. And for all we know, it may be enough for our needs, or it may not. We do not know.

In the words of Ahab to the King of Damascus, 'Let not him that putteth his armour on boast himself as he that taketh it off'. Today's conference will give us an admirable opportunity to polish it up!

An historical perspective

Professor George Teeling Smith
Office of Health Economics

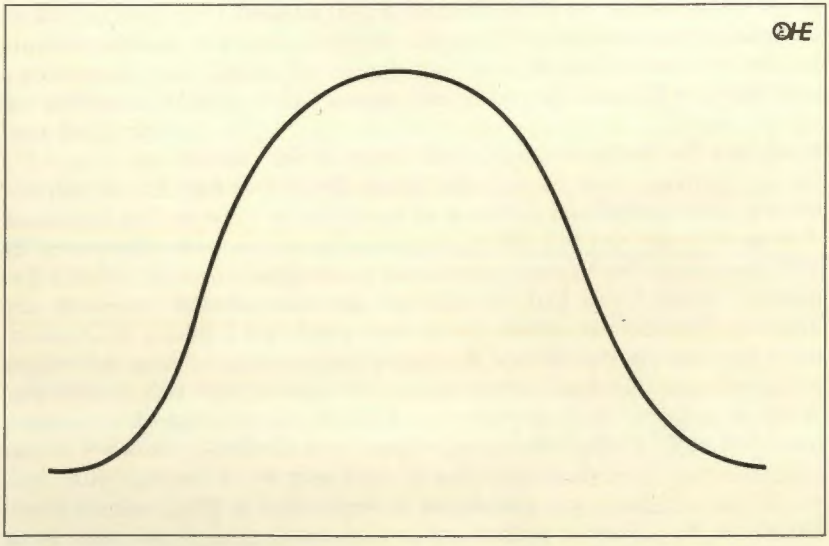
Four years ago, at a previous OHE symposium in this same splendid setting, I showed a slide of what has been nicknamed the 'Teeling Smith All-Purpose Growth and Decay Model' (Figure 1). I make no apologies for basing my brief presentation this morning on the same underlying premise. It is indeed an all-purpose model. The message from it is that all living organisms and all social structures develop in essentially the same pattern. After slow early growth, there is a period of rapid development, which in turn flattens out and leads on to a phase of decline and eventual death. This basic pattern applies to such diverse examples as a great human being, such as Winston Churchill, a disease such as smallpox, or even horse-and-buggy transportation. Each reaches an apogee, and then inevitably goes into a decline.

However, such growth and decay curves do not exist in isolation. As great men and women die, so others rise to take their places. As diseases are conquered, others emerge to present new medical problems. And the horse-and-buggy became obsolete because the motor car was developed to supersede it.

My thesis today is that the growth of pharmacology over the past two thousand years can be seen as a series of similar growth and decay models.

The first of this series of curves dates back to Galen, who died in the year 200 AD and who gave his name to 'galenicals' – the tinctures, mixtures,

FIGURE 1 **The all-purpose growth and decay model**



extracts and powders prepared from mainly vegetable drugs. Such preparations dominated the medical scene until as late as the end of the 19th century. They had, of course, gradually become purer and more systematically prescribed and dispensed, until their professional handling was in a sense formalised in Britain by the establishment of the Apothecaries' Society in 1617. As an aside, the apothecaries were later to concentrate more on making diagnoses than making medicines, and were eventually to become the general medical practitioners of the 19th century. Their role as the compounders of medicines was then taken over by the chemists and druggists, who in turn started to 'professionalise' themselves in Britain by the formation of the Pharmaceutical Society in 1841. Individual pharmacists were still concerned with the manufacture of medicines until the 1940s; but since then their role in turn has changed and they now concentrate on the distribution of remedies and giving advice on them. Manufacture is now predominantly in the hands of the pharmaceutical industry.

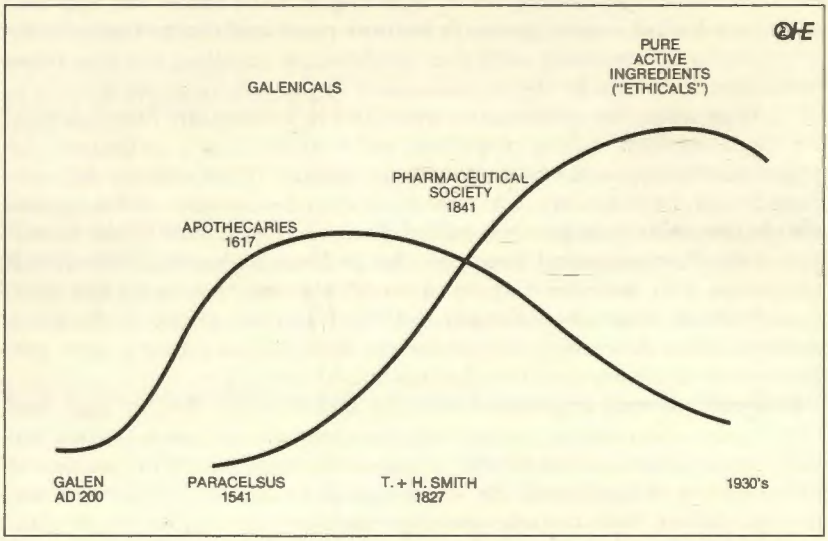
However, several centuries earlier Paracelsus, who died in 1541, had envisaged a different and more scientific approach to pharmacology. He has been described as one of the 'soundest of physicians and shrewdest of compounders of medicines'. He wrote that alchemy was 'neither to make gold nor silver, but to make the supreme sciences and to direct them against disease'. His concept of the synthesis of medicinal chemicals was well ahead of its time, because the next development, starting in the 19th century, was to be the extraction and purification of the active principles from naturally occurring drugs.

My own great-grandfather, Henry Smith, and his brother, Thomas, were pioneers in this work in a business which was founded in 1827. A history of the business written a century later records that 'the brothers investigated opium, aloes, tea, ginger, capsicum, podophyllum and the jalap and scammony resins. They prepared the then less well known alkaloids of opium, including codeine, as well as salicin, capsicin, gingerin and podophyllin'. Early firms of manufacturing chemists and druggists, such as theirs, were gradually to emerge as the forerunners of the pharmaceutical industry as we know it today. By the end of the 19th century these pure active, naturally occurring chemicals were being formulated into proprietary preparations, including the recently developed compressed tablets, and many were being sold on prescription-only under the manufacturers brand name. Because these preparations were advertised only to doctors they became known as 'ethicals', a term which was never very rational and which has how happily fallen into disuse.

Thus the original galenicals started to give way to these new branded medicines based on pure active ingredients, and this development is illustrated in terms of my growth and decay curves in Figure 2.

The next phase of development brings us on to the true therapeutic revolution of the 20th century. This took place in the 1940s, 1950s and 1960s. hence the modern pharmaceutical industry as we know it today can be seen as a third phase of pharmacology, which dates from less than 50 years ago. It is largely based on the discovery and development, envisaged by Paracelsus 400 years earlier, of specific synthetic pharmaceutical chemicals. The antecedents of the 20th century therapeutic revolution, however, date back more directly to the development of the germ theory by Pasteur in the

FIGURE 2 **Early developments in medicines**



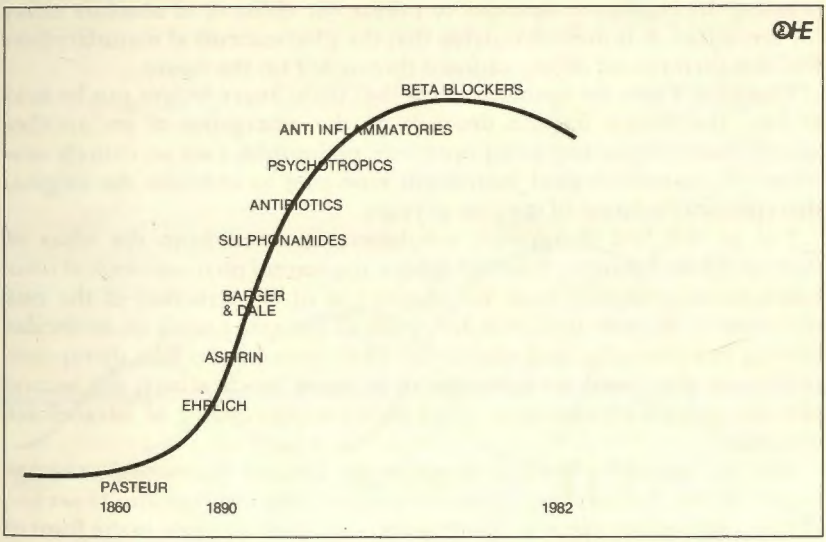
1860s. This led to the dream by the chemist Ehrlich in the 1890s that it should be possible to find a 'magic bullet' which would attack the invading germs without harming their human host.

This was followed by many specific developments in biochemistry. For example, Barger and Dale working in the Wellcome Research Laboratories discovered the chemical basis for the transmission of signals in the autonomic nervous system. Progress such as this laid the basis for modern synthetic medicinal chemistry. Ehrlich's dream was eventually fulfilled by the development of the anti-bacterial Prontosil in Germany in 1935 and of the sulphonamide 'M and B 693' in Britain shortly afterwards. These discoveries were followed by a plethora of synthetic medicinal chemicals working on all manner of control systems within the body. Figure 3 shows this new phase of growth in pharmacology in the form of another growth curve. This took over where the second curve, based on the isolation of pure naturally occurring ingredients, started to tail off.

Bringing the story up to the present time, Cassandras in the industry now argue that the wave of pharmacological innovation of the 1950s and 1960s seems to be petering out, and that the industry is facing such a hostile environment that its growth must inevitably be stifled. They draw attention to the extent of government regulation surrounding the testing and marketing of new medicines; the controls on prices and profits; the restrictions on sales promotion; the erosion of patent life; the weakening of brand name protection and the pressures for generic medicines; and the general consumerist hostility towards pharmaceutical innovation. All of these adverse influences, shown in Figure 4, threaten to stifle future innovation, sending pharmacological innovation into decline.

Indeed at the 1978 OHE symposium on 'Medicines for the year 2000', Brian

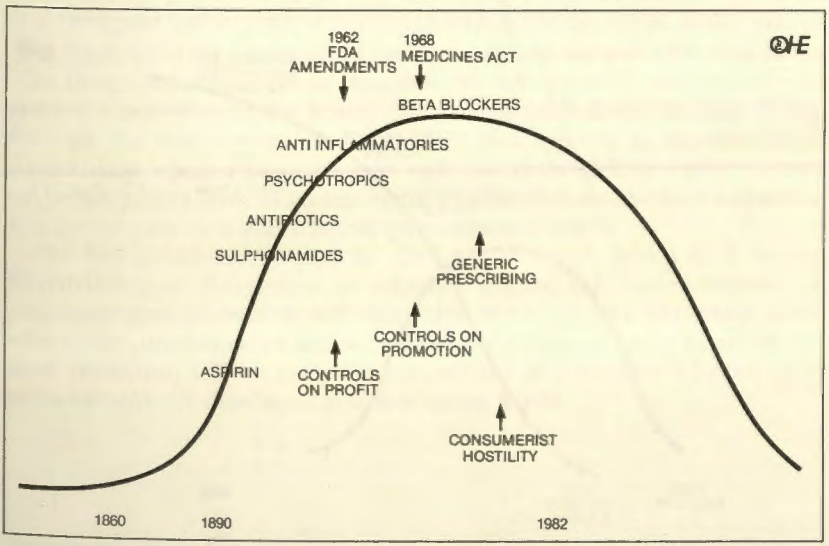
FIGURE 3 **'The first therapeutic revolution'**



Cromie predicted that under these adverse influences his company's rate of innovation might have reached zero by the year 1988.

In this sense, those in the pharmaceutical industry are sometimes accused of 'crying wolf'. But it is not surprising that they should do so. There are indeed a pack of irritable wolves snapping at their ankles: for example, governments wanting cheap drugs; social security schemes and

FIGURE 4 **'The first therapeutic revolution'**



even some pharmacists calling for generic substitution; and consumerists pressing the regulatory agencies to pursue the chimera of absolute safety for medicines. It is understandable that the pharmaceutical manufacturers feel that their record of innovation is threatened for the future.

However, I take the optimistic view that these angry wolves can be held at bay. The reason for this depends on the emergence of yet another growth curve. According to my optimistic philosophy, I see an entirely new phase of pharmacological innovation emerging to overtake the original therapeutic revolution of the past 40 years.

Just as the first therapeutic revolution stemmed from the ideas of Pasteur, Ehrlich, Barger, Dale and others, the second pharmacological revolution stems primarily from the elucidation of the structure of the DNA molecule by Watson and Crick and from all the other work on molecular biology in Cambridge and elsewhere. Thus whereas the first therapeutic revolution was based on intercellular or tissue biochemistry, the second pharmacological revolution is based on an understanding of intracellular chemistry.

I do not intend to dwell on its potential, because that would pre-empt some of the forthcoming presentations to this symposium. However, Figure 5 shows that the new developments are likely to come in the form of progress against the virus diseases, the cancers and the autoimmune diseases such as early onset diabetes, multiple sclerosis and possibly rheumatoid arthritis.

In conclusion, Figure 6 summarises the brief history which I have tried to expound. In my view there have been three clear phases of pharmacological development since the days of Galen – first, galenicals; second, preparations based on pure active ingredients; and, third, the synthetic pharmaceutical chemicals of the latter part of the 20th century. Each has reached an

FIGURE 5 **Prospects for the 1990s**

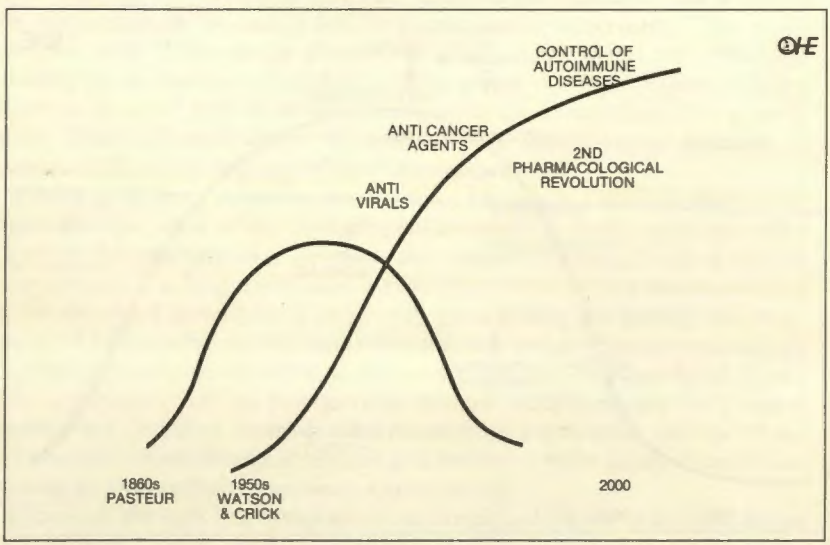
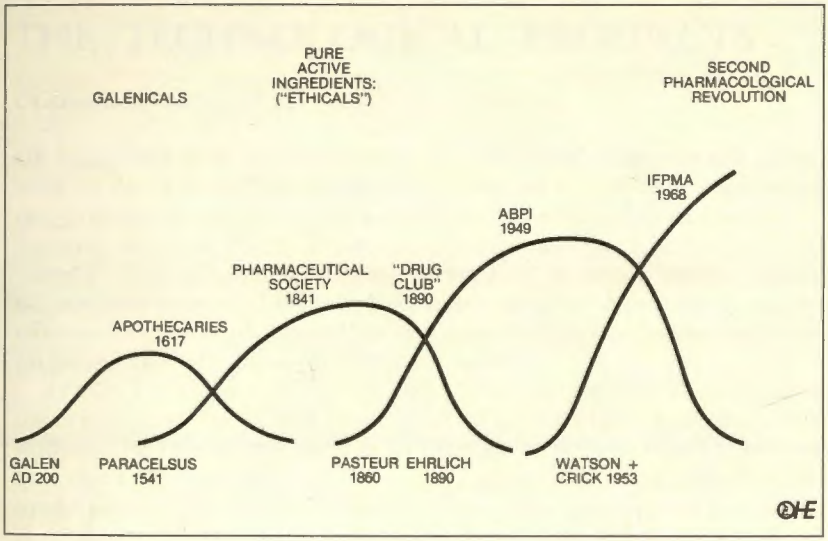


FIGURE 6 **Pharmaceutical phases**



apogee and the first two have already gone into a decline. My proposition is that we are on the verge of a fourth phase, which I have called 'The Second Pharmacological Revolution'. This will take over and provide the means of controlling many of today's unconquered diseases as products of the original therapeutic revolution become available as cheap patent-expired generics.

(It is of interest to note, in passing, that the manufacturers who have emerged in the second and third phases of this history have organised themselves in much the same way as the Apothecaries and the Chemists and Druggists had organised their professional structure at earlier stages. The Manufacturing Chemists of the 19th century formed what was called 'The Drug Club' in Britain in 1890, and this subsequently evolved into the present Association of the British Pharmaceutical Industry in 1949. Today, through the International Federation of Pharmaceutical Manufacturers' Associations which was founded in 1968, the research-based pharmaceutical industry has a body to set minimum professional standards of behaviour and to represent it at international governmental level.)

The key question, however, is whether there will indeed be a Second Pharmacological Revolution or whether instead the forces opposed to pharmaceutical innovation will succeed in stifling it. The important issues which this question raises are not simply the subject of today's symposium; their resolution will be a major determinant of tomorrow's health prospects for both the developed and developing world.

SESSION II

THE TECHNOLOGICAL PROSPECTS

Chairman Professor Hans Dengler, *Bonn University*

On being invited to act as chairman for the second session of this symposium on the Second Pharmacological Revolution my initial reaction was in fact to question the appropriateness of the title that had been given to the meeting. More specifically, my doubts were focused on the use of the terms 'second' and 'revolution'. Having listened to Professor Teeling Smith's introductory remarks, however, I am now convinced that to think in terms of a *second* phase of pharmacological advance is fully justified by the historical perspective which emerged from his paper.

As I am a clinician and, further, one who comes from Heidelberg where medical reports dating back to 1864 can be found, I have spent some time studying the role of therapeutics in practice. It is interesting to note just how many different drugs were given to patients before the 1900s. Yet even by the turn of the century the lack of therapeutic gain as well as the complete absence of any treatment whatsoever for many severe diseases persisted – it was a time of therapeutic nihilism. It seems to me, therefore, that the early 1920s may be considered as the beginning of true therapeutic advance and, given subsequent developments, I am prepared to drop my objection to the term *'second'* revolution.

Turning to the use of 'revolution' itself, my unease stemmed from the fact that conventional definitions of the word usually convey a sense of change involving *violent* disruption. But, again, having heard the opening addresses from The Earl of Halsbury and Professor Teeling Smith I can accept that revolution is appropriate in the context of the speed and magnitude of the advance that has taken place, and seems likely to continue, in our understanding of and ability to control disease.

Prostaglandins and antivirals

Dr John Vane
The Wellcome Foundation Ltd

It is sometimes said that the major discoveries have already been made and that there is nothing important left to find. I regard this as altogether too pessimistic. I believe that today we only know one tenth as much about the important biological processes as we shall know in 50 years time. There are plenty of ideas and plenty of things left to discover. The trick is to find the right path from one to another.

The medicines of today are based upon thousands of years of knowledge, accumulated from folklore, serendipity and scientific discovery. The new medicines of tomorrow will be based on the discoveries that are being made *now* arising from fundamental research in both academia and the pharmaceutical industry.

In the time available to me, there is no way that I can do more that outline the developments in antivirals and prostaglandins. I hope that I can convince you that the promise in both fields is bright.

Let me start with the antivirals and I wish to concentrate on two: interferon (IFN) and acyclovir. The interferon story has, of course, hit the headlines with respect to cancer but I want to deal with its antiviral activity, the property that was first recognised by Isaacs.

Workers at the Common Cold Research Unit at Salisbury first showed that leucocyte interferon will prevent common colds. Later, they showed that IFN, purified on a monoclonal antibody, also was effective. This monoclonal antibody only retains six out of the eight peptides present in lymphoblastoid interferon. Later still they showed that interferon alpha 2 made by recombinant DNA technology is effective. These results are full of promise. Respiratory infections remain very common; they are not much influenced by rising standards of living and hygiene. Moreover, the number of virus types is so great that a vaccine approach is daunting. Finally, interferon given via the nasal route is effective in preventing common colds and can be safely administered. Also, given in this way, it does not cause the flu-like symptoms that occur when large doses are given parenterally for the treatment of cancer. Who would have predicted, during the first pharmacological revolution referred to by Professor Teeling Smith, that a protein sniffed up the nose would prevent and may cure the common cold?

New peptide and protein mediators or transmitters are being discovered almost daily and the interferon story is no exception. There are three sorts of interferon, α, β and γ. α IFN is produced in virus-infected cells and is a potent antiviral agent. This is most clearly shown in experiments in mice where high titre antibody to interferon results in a disastrous increase in pathogenicity of many viruses. This is supplemented by clear evidence of antiviral effectiveness in herpes simplex, varicella zoster and respiratory virus infections in man. There is as yet no clear answer to the question, how many α interferons are there? At least eight peptides are present in lymphoblastoid interferon, but gene cloning has revealed about double

that number of genes, but so far not all the gene products have been identified under physiological conditions *in vivo*. α interferons are produced by non-specialist lymphocytes and by epithelial cells. β interferon is produced by fibroblasts: so far only one species has been definitely identified, although messenger RNA for a second species has been described. γ interferon is stimulated by antigens and produced by T cells of the immune system. It is a marker of such T cell stimulation but, like all interferons, is an active antiviral substance. The view is increasingly emerging that interferon plays a very important regulatory modulating role in the immune system, as well as acting as an effective antiviral molecule. One interesting effect it has is to increase the expression of HLA antigen which is a recognition signal for T cells.

Interferon has played an immense facilitating role in recombinant DNA technology. Before it was a rare and expensive commodity and then by gene cloning it could suddenly be produced in quantity. It is too large (160 amino acids) for chemical synthesis, yet it is small enough to fit easily into a bacterial plasmid and it is also very stable to pH changes and to proteases. A problem with genetically engineered IFN is that it is a single species, whereas naturally a whole series is made. Lymphoblastoid interferon, for example, has been shown to be more effective at inhibiting human mammary tumour cell growth in nude mice than $\alpha 2$.

It seems certain that over the next 10 years the place of interferon in medicine for the control of virus infections will be found and its place in cancer therapy will be greatly clarified. Perhaps even more important, it will have given us an insight into the regulatory and effector mediators of the immune system.

A new era of antiviral chemotherapy is also starting in the area of custom-made therapeutic agents. Until recently the few antiviral agents that were active against viruses, like Marboran for vaccinia and smallpox, and Idoxuridine and Vidarabine for all DNA viruses, were not truly selective. They inhibit virus growth because of the greater turnover of viral compared with cellular DNA. The change in attitude and prospects for antiviral chemotherapy is due in large measure to the discovery by Wellcome of acyclovir. The team included John Bauer, the virologist, Howard Schaeffer, the chemist, and Trudy Elion, who with her colleagues unravelled its mode of action. Acyclovir has three levels of selectivity: first, it is preferentially absorbed by virus-infected cells. Second, it is phosphorylated preferentially to the monophosphate by a viral encoded enzyme. Third, it is more active, i.e. has a greater affinity for viral DNA polymerase than for cellular DNA polymerase. The result is a highly selective action against the narrow spectrum of viruses that are susceptible, for example, herpes simplex 1 and 2; varicella zoster and probably Epstein Barr and hepatitis B virus antigen. With this high selectivity of antiviral effect goes a very low level of toxicity which gives it a very favourable therapeutic index. Acyclovir is a more effective drug for treating herpes simplex and varicella zoster infections. Its effectiveness is most dramatically apparent the more serious the disease. Thus, primary infections, like primary genital herpes, herpes neonatorum and varicella pneumonia are where the results are most dramatic, especially if the drug is given intravenously. Oral treatment is also effective in some types of infection. Similarly, when latent virus recurs in the immuno-

compromised and gives serious recrudescent disease, then again the drug has marked effects. It is also effective in milder labial or genital recurrences in normal subjects or in varicella zoster. For local treatment, a modified aqueous cream has shown marked superiority over a polyethylene glycol-based ointment in animals and is also more effective in man.

The successful development of this drug has already been followed by the description of a number of other effective drugs against herpes viruses, for example, phosphonoformate, found to be effective against labial herpes, bromovinyl deoxyuridine and 2-fluoro-5-iodocytosine. Whether or when these will reach the market is uncertain.

Another type of antiviral action is illustrated by the antirhinovirus compound, 2,6 dicholoroflavan. This is immensely active having an ED_{50} of 0.007 μM, making it the most active antiviral compound known. It acts by combining with virus, indeed, to a viral protein, and it does not prevent adsorption to the cell or penetration into it. Nor does if affect viral uncoating, yet it completely inhibits viral RNA replication. It was not effective when given orally for the prevention of the common cold in challenge studies carried out at the Common Cold Research Unit, but it may work intranasally; time alone will tell.

As a result of advances in molecular aspects of virology, new targets for antiviral action are being identified. In particular, viral specified enzymes can be cloned, produced in large quantities and studied for antagonists. It seems certain that this approach will lead to new antiviral drugs.

I want now to turn to the complex field of prostaglandins for these provide a good example of rapid progress in scientific knowledge (with a little help from serendipity) giving the potential for new therapy. They were discovered some 50 years ago and first characterized by Sune Bergström, the 'father' of prostaglandin chemistry. Since then, thousands of chemical analogues have been synthesized, in the largely frustrated hope that a useful drug would emerge.

In the mid 1960s, we knew that PGE_2 and $PGF_2\alpha$ were formed by oxidation of arachidonic (AA) acid but there was not much known of their function. Nevertheless, in these early days, hopes for new drugs were bright and on the assumption that PG's did *some* good, analogues of E_2 and $F_2\alpha$ were made, only to find that they had all sorts of important side effects, including fever, pain at the site of injection, formation of oedema and diarrhoea.

An explanation for the lack of success came in 1971 when we showed that aspirin prevented the biosynthesis of PG's and proposed that this was the mechanism of therapeutic activity. That the aspirin-like drugs work in this way is now largely accepted, but it carries the corollary that all PG's are not 'good boys' and some of them are 'bad boys' which are better eliminated. This important change in emphasis has led my own thinking to compare the oxidation of polyunsaturated fats in the body to the same peroxidative process which goes on in foods without preservatives, such as butter – as we get older, so we tend, like food, to go 'off' – a little 'rancid', getting more smelly, more disagreeable and less attractive all the time. What we need are more anti-oxidants as preservatives.

Over the last ten years, mainly through the brilliant work of Bengt Samuelsson and his colleagues, as well as my own team at Wellcome, we have learnt a lot more about the oxidation of fats in the body. Other arachi-

donic acid metabolites have been identified including thromboxane A_2, prostacyclin and the leukotrienes (first known as slow reacting substances).

The identification of the leukotrienes as metabolites of arachidonic acid and their putative role as mediators of inflammation and asthma opens a whole new area of anti-inflammatory research. Inhibitors of not only the cyclo-oxygenase enzyme (such as aspirin) which leads to the prostaglandins and thromboxanes but also of the lipoxygenase enzyme (which leads to the leukotrienes) should have a better anti-inflammatory profile than aspirin, corresponding more closely to that of the steroids. And it is interesting that the action of the anti-inflammatory steroids are now firmly linked with the arachidonic acid cascade. It has been shown in several whole cell or organ systems that the steroids inhibit phospholipase A_2, the enzyme responsible for cleaving arachidonic acid from its phospholipid stores in the cell membrane. This will, presumably, lead to a reduction in *all* the products of arachidonic acid, including the leukotrienes, nicely explaining why steroids but not aspirin-like drugs are effective in asthma.

Most exciting is the discovery by Rod Flower at Wellcome and others that the action of steroids in this respect is transmitted by a 'second messenger' – a protein called macrocortin secreted by cells in response to steroid action. It is macrocortin which directly inhibits the enzyme phospholipase. Elucidation of its structure and synthesis of peptide analogues will surely be another important lead in the treatment of inflammatory diseases, including asthma.

Turning now to another exciting area, prostacyclin (PGI_2) is generated by the vessel wall (especially endothelial cells), is a potent vasodilator, and the most potent endogenous inhibitor of platelet aggregation so far discovered. Prostacyclin inhibits platelet aggregation by increasing cyclic AMP levels. Another substance with the same fatty acid precursor (arachidonic acid) is thromboxane A_2 (TXA_2) which is made by platelets, leads to their aggregation and potently constricts arterial muscle.

We have developed the hypothesis that it is a balance between formation of PGI_2 by the vessel wall and of TXA_2 by the platelets which controls haemostasis. Some types of vascular disease may be associated with a reduced prostacyclin formation, in which case prostacyclin could be used as a kind of 'hormone replacement therapy'.

The vessel wall can synthesize prostacyclin not only from its own endogenous precursors, but also from prostaglandin endoperoxides released by the platelets, thus suggesting a biochemical co-operation between platelet and vessel wall. Adherence of the platelet to the vessel wall, known to be one of the first responses to injury, could well provide the close proximity that would be needed for such 'co-operation'.

Prostacyclin is available as a stable freeze dried preparation (Epoprostenol: 'Flolan', Wellcome) for administration to man. Intravenous infusion of prostacyclin in healthy volunteers leads to a dose-related inhibition of platelet aggregation, dispersal of circulating platelet aggregates, arteriolar vasodilatation, increases in skin temperature, facial flushing and sometimes headache.

Extracorporeal circulation of blood brings it into contact with artificial surfaces which cannot generate prostacyclin. In the course of such procedures thrombocytopenia and loss of platelet haemostatic function occur

and make an important contribution to the problems associated with charcoal haemoperfusion or prolonged cardiopulmonary bypass in man.

Platelet damage and thrombocytopenia were prevented by prostacyclin in various animal models of extracorporeal circulation and this has now been confirmed in man. Roger Williams and his colleagues have now made almost 200 charcoal haemoperfusions on a daily basis using prostacyclin for platelet protection in the treatment of 76 patients with fulminant hepatic failure. Remarkable survival rates (65 per cent) were obtained in the 31 patients who had been referred early and in whom the serial haemoperfusion was started whilst signs of grade III encephalopathy were still evident (sleeping most of the time but rousable with incoherent speech and marked confusion). In addition, cerebral oedema developed less frequently in this group than in those patients in whom haemoperfusion was started later when signs of grade IV encephalopathy were already apparent (not rousable but may or may not respond to painful stimuli). The authors thought that this was probably the major factor in their improved survival. In this latter group, 20 per cent survived, so that the overall survival rate from the 76 patients was 38 per cent. These results (especially those treated early) compare very favourably with a survival rate of 15 per cent in patients under standard intensive care measures.

Several double blind clinical trials of prostacyclin in cardiopulmonary bypass have been published. The treatment groups showed a preservation of platelet number and function, with a reduction in the blood loss in the first 18 hours after operation. In the trial by Longmore and his colleagues the blood loss was halved and the reduction was statistically significant. The heparin-sparing effect of prostacyclin was confirmed and the vasodilator effects were not troublesome.

As first shown in dogs, prostacyclin can safely be used in man to replace heparin as the sole antithrombotic agent during haemodialysis and may well be advantageous when anti-coagulation is contraindicated. Indeed, prostacyclin has been safely used instead of heparin during dialysis in more than 50 patients.

In peripheral vascular disease, prostacyclin was of benefit in open trials in terms of relief of ischaemic pain and ulcer healing. Placebo controlled double-blind trials are now in progress and the results of the first to be reported by Belch and Prentice are encouraging. Dramatic differences were observed between placebo and prostacyclin-treated patients at 5 days, 1-month and at the 6-month follow-up.

Prostacyclin also induced significant and long-lasting improvements in Raynaud's phenomenon and the striking reductions in the frequency, duration and severity of the disease seen in open trials have been confirmed in a double-blind study.

Richard Gryglewski and his colleagues in Cracow were the first to demonstrate the beneficial effects of infusion of prostacyclin in ischaemic disease of the legs. They have now obtained dramatic improvements following prostacyclin infusion in 10 patients with ischaemic stroke. Patients with transient ischaemic attacks and haemorrhagic stroke were excluded. With prostacyclin treatment there was a reversal of symptoms strikingly sooner in all ten patients than could have been expected and in six patients during the first six hour infusion. One patient died two weeks later of a

second stroke, but the other nine have maintained return of function for (so far) up to 11 weeks.

Clearly, there are many clinical conditions which may respond to prostacyclin treatment and its place in therapeutics will be defined by controlled clinical trials in the next few years. These conditions include pre-eclamptic toxaemia, haemolytic uraemic syndrome, the thrombotic complications associated with transplant rejection, the prevention of tumour metastasis and treatment of pulmonary embolism. The role of reduced formation of endogenous prostacyclin in the initiation of atheroma is also an important area for future research.

There is also evidence that prostacyclin has a general, as yet undefined mechanism of cell protection. For instance, prostacyclin reduces infarct size in some experimental models of myocardial infarction and is of benefit in endotoxin shock. Interestingly, the addition of prostacyclin during the separation from blood and the subsequent washing of platelets improves their viability *in vitro* from about 10 hours to 72 hours. These studies suggest a potential wider therapeutic role of prostacyclin in cell or tissue preservation.

The possible difficulties of using an unstable substance intravenously as a medicine, together with the desire to separate from each other the three main activities (vasodilator, anti-platelet and cytoprotective) of prostacyclin has led to a world-wide search for stable and more specific analogues. The clearest separation of activities has been achieved with analogues which inhibit gastric acid secretion and gastro-intestinal ulceration induced by indomethacin. These lack platelet anti-aggregatory activity and have little effect on the cardiovascular system, but are potent as anti-secretory, anti-ulcer agents.

There are other ways of displacing the balance between prostacyclin and thromboxane A_2. For instance, specific inhibitors of the enzyme which generates thromboxane A_2 should swing the balance towards the anti-thrombotic side, especially if endoperoxide metabolism is diverted to prostacyclin formation. In this respect, a selective thromboxane synthetase inhibitor has theoretical advantages over aspirin as an anti-thrombotic agent, for aspirin has the potential to reduce prostacyclin production as well.

Research into the fatty acid precursors in our diet may also lead to new, simple, but potentially valuable agents. In some communities, such as the Greenland Eskimos, the main dietary precursor for prostanoids is eicosapentaenoic acid (EPA) from the predominantly marine diet that they eat. This could give rise to TXA_3 and PGI_3, the properties of which may tip the balance of the prostacyclin/thromboxane system towards the anti-thrombotic side. Such an imbalance could account for the lower incidence of heart attacks in Greenland Eskimos and also for their prolonged bleeding time.

To conclude – there are several enzymes in the cascade leading to the oxidation of fatty acids in the body which are susceptible to selective inhibition. Even the composition of the fats in cell membranes may be changed beneficially to reduce disease.

Release of the fatty acid AA itself can be inhibited by steroids, so all the products will be affected. The discovery of macrocortin offers another therapeutic avenue to be explored.

Aspirin-like drugs only affect cyclo-oxygenase but a new group of substances is on the way which will inhibit both lipoxygenase and cyclo-oxygenase, giving a better anti-inflammatory profile which may extend into myocardial infarction and asthma. Within the cyclo-oxygenase pathway there is also the opportunity of selective inhibition of thromboxane formation by newly synthesized substances. And then, the advent of prostacyclin has led to exciting concepts, especially in a kind of hormone replacement therapy.

Indeed, there is a lot of exciting work still to be done and I have never been so confident that in the next 20 years we shall see a further substantial attack on the disease process, so that we don't go rancid quite so quickly as we mellow with age!

Medicine and genetic engineering

Dr William Hubbard Jr
The Upjohn Company, USA

From the viewpoint of medicine, genetic engineering is a technology for producing a great variety of biologically potent polypeptides and proteins; characterised by an exquisite specificity and available in quantities that are theoretically unlimited. These molecules have heretofore been very difficult or not feasible of chemical synthesis and therefore have been available in only limited amounts from natural sources, and in less-than-pure forms. The two principle techniques for producing these biogenic polypeptides and proteins are the recombination of genetic information from dissimilar organisms and the fusions of dissimilar cells to form a monoclonal hybridoma that is viable and differentiated *in vitro* over an extended time.

Five principle classes of these agents are at present either at laboratory stage of development or in actual clinical use:

Peptide Hormones	Albumins
Immunoproteins	Enzymes.
Glycoproteins	

Peptide hormones

Of the polypeptide hormones, insulin and growth hormone are the most widely available. Neither of these agents is in general use but each has been carried far enough in clinical research so that it is now evident that the hormones derived through genetic engineering (in this case through genetic recombination) retain the full activity of the same hormone derived from natural sources. It is an interesting coincidence that during the time of introduction of insulin from genetic engineering, the bio-chemists succeeded in modifyng porcine insulin to its human molecular form. Although tangential to the subject of this review, it is important to recall that the power of existing technology such as organic synthesis has not been preempted by the development of genetic engineering.

From a research viewpoint, one of the most interesting developments has been the successful cloning of an active fragment of adrenocorticotrophic hormone (ACTH) which contains 24 of the 39 amino acid residues of the natural hormone. The physiologic activity of this fragment appears to be quite different from that of the natural hormone. For the future, the preparation of analogs of natural polypeptide hormones may prove to be the most exciting and important therapeutic development in this field. At the present time, the medical utility of this set of compounds is confined largely to replacement therapy, analogous to the more traditional use of insulin or thyroid hormone. It is of some interest to observe that hormonal deficiencies, although not in any sense rare diseases, are neither to be counted among the more common diseases. The total number of patients throughout the world who can be benefited by supplemental therapy from

polypeptide hormones is probably of such an order of magnitude that only a very few producers of these agents through genetic engineering would fully satisfy the demand.

Glycoproteins

A group of glycoproteins have become available through recombinant genetic techniques which have heretofore been unavailable through synthesis and available only in small and impure samples through extraction. The best known of these glycoproteins is the set of interferons. The early promise of general utility in cancer therapy of interferons derived from human leukocytes has been moderated as experience has grown with the further clinical research involving both fibreblast and leukocyte derived interferons. Work continues both in the field of cancer chemotherapy and in the management of viral infections. Under clinical experimental conditions, both humans and animals have been demonstrated to have some protection from viral infections following the administration of interferon. Although the potential utility of such a use is very great, it is not possible at this time to predict, with any degree of certainty, what the actual utility of interferons in the prevention or treatment of viral diseases may be.

In addition to the interferons, the glycoproteins form cytokines and particularly lymphokines that have very important controlling effects on the vigour with which the immunophagocytic cellular response occurs. The complexity of the system is unusual in that over 100 lymphokines have been identified. The opportunity for the future is to utilize these glycoproteins to modify the host response so that an optimum defence is induced against intruding non-self materials. These glycoproteins are most successfully produced, at the present time, through techniques of recombination.

Albumins

Human serum albumin has been successfully expressed through recombination and for the future offers an important new source of plasma expanders of human molecular-type. To my knowledge, clinical trials have not been undertaken at this point in time with serum albumin but there is every reason to expect that it will have an important utility.

Enzymes

Enzymes represent a relatively unexplored area of medicinal therapy. The importance of enzymes in the chemistry of living systems is very great and offers equally great theoretical opportunities for utilities that have heretofore hardly been explored. It is, of course, true that the pro-enzymes called factors eight and nine have been used in patients with haemophilia as a form of enzyme replacement therapy. More recently, urokinase and streptokinase have been utilised as activators of the plasminogen system in successful clinical trials that finally demonstrated their utility as thrombolytic agents. I apologise for a personal reference at this time, but in the late 1940s I was a very junior member of the group that did the initial work with streptokinase in humans and had the doubtful distinction of making the first attempt to observe thrombolysis in humans as a result of the activity of streptokinase. Suffice it to say that the impurities present at that time gave the material a physiological profile indistinguishable from triple typhoid

vaccine. The availability of enzymes through genetic engineering that are extremely pure and highly specific could open an entirely new strategy of therapy; but such theoretical utility is at the present time entirely speculative.

Immunoproteins

The production of antigens by recombinant techniques for utilisation in active immunisation is becoming a reality. A portion of the genome of the foot-and-mouth disease virus has been replicated through recombination and has proven to be an effective immunogen. One of the problems of vaccination against viral diseases has, of course, been the relative difficulty of assembling enough purified protein from killed viruses. Vaccination with attenuated viruses has proven to be extremely valuable but carries with it an obvious residual risk of back mutation and of idiosyncratic susceptibility. By utilising partial viruses, the problem of infectivity could be eliminated while retaining the antigenic potency of the intact virus. This same approach offers promise in the development of fragments of toxins which provide clinically effective immunisation without the undesirable side effects that accompany the use of the whole toxin. Finally, there is the theoretical possibility of identifying antigens that are specific to the malignant cell. Such antigens, theoretically, would provide a means of active immunisation against the tumour cell without the risk associated with the use, as a vaccine, of an intact tumour cell or major portions of it.

Of the immunoproteins derived from techniques of genetic engineering the antibodies prepared through fusion of a host plasma cell and a lymphocyte are surely the most widely used agents in the realm of diagnosis and promise rapidly to become widely utilised in therapy. When one recalls that it was only seven years ago that Milstein and Kohler, working at Cambridge University, first described the successful production of hybridomas, it is remarkable that both the general field and the specific utilities have become so broadly evident in so short a time. A great many problems remain in this area – not the least of which is finding human cell lines that are stable when fused with immuno-competent lymphocytes. Murine hybridomas continue to be the principle source of specific antibodies and it is inevitable that an inherent risk exists of sensitisation to foreign protein in the utilisation of such a non-human cell line.

Patients suffering from B-cell lymphomas appear to have a true monoclonal neoplasm. In such patients, the antibodies derived from hybridomas to the B-cell have had a dramatic effect in inducing clinical remissions in this relatively rare disease. The demonstration, however, raises the real possibility of developing other such organ-specific antibodies. Unfortunately, many, if not all, solid tumours are heterogenous rather than monoclonal, suggesting that an array of antibodies appropriate to the individual tumour will be needed. Further complicating the task are the probable differences in antigenetic profile during the several stages of the tumour cell's life cycle.

A variety of T-cell specific antibodies have been produced – particularly the OKT system. The OKT antibody has given early indication of being effective in the prevention of graft versus host disease following organ transplant. A more recent report of the successful developments of an anti-HLA

antibody suggest that we are at the beginning of a set of developments which may lead to an array of specific antithymocyte antibodies that are theoretically capable of inhibiting the set of reactions that ultimately result in the rejection of transplants.

The enhancement of the host's defence system is a general mechanism utilising hybridoma-derived antibodies. Baldwin and his group at Nottingham University have led the work in the activation of natural-killer T-cells. The development of antibodies utilising naturally-occuring auto-antibodies as the antigen has reached the point that it is not unreasonable to expect that a number of the so-called autoimmune diseases may be approachable by this technology.

The replacement of antibodies in patients with an immuno-deficient state is a direct possibility and would provide for the maintenance of such patients with replacement therapy, not unlike that provided to patients with diabetes. In a kind of auto-replacement it appears possible that one may successfully remove a bone marrow, kill the leukemic cells by activated T-cells that respond to the leukemia cells but spare the early stem cells. The patient may then be subjected to radical haematocyte eradication. One may then re-transfuse the stem cells with a subsequent derived population of cells that is normal. Schlossman, and his co-workers at Harvard, have reported on such a successful effort.

The utilisation of specific antibodies as carriers of cytotoxic agents has been widely discussed. Jonathan Uhr, and his associates at the University of Texas in Dallas, have reported on the linkage of ricin with tumour specific antibodies and the resultant selective elimination of the tumour system. As with all such efforts, the lack of tumour cell markers that are truly unique, exposes the possibility of delivering toxic materials to other than the targeted population. Since these antibodies will complex and ultimately be phagocytised, the risk also exists that one may create widespread damage of the macrophage cell system even in those cases where the toxin-linked antibody is quite specific. Nevertheless, the utilisation of specific antibodies as drug delivery systems at a molecular level has so many attractive advantages that it will undoubtedly be a field of major research effort in the future.

The use of radiolabeled specific antibodies from hybridomas as diagnostic tools represents the largest present utility of these agents. Once again, Robert Baldwin and his group at Nottingham have led in this field. Rapid and accurate diagnosis may, for a long time to come, be the most important contribution of biotechnology to medicine. These agents are already widely available and being increased almost daily in their number. Where the antibodies are 'tumour specific', a biological method of identification of malignancy becomes available to supplement, if not supplant, the traditional histologic observations. In infectious diseases, the availability of such specific antibodies would make the prompt identification of infective organisms more readily available than current technology.

Today's speculation seems to be rapidly becoming tomorrow's commonplace. Rather than extend this inventory, I would simply assert that the utility of the same radiolabeled antibodies in studying natural biologic events may open broader fields for diagnostic and therapeutic intervention than have been imagined by considering direct application of these antibodies themselves.

Discussion

In discussing the inter-relationships of genetic engineering and medicine, it is easily possible to create the misimpression that the very foundations of medicine are being changed. In point of fact, the major causes of premature death and disability in the world today may not be much affected by this bio-technical revolution. While the individual physician must be concerned primarily with the individual person who is a patient, medicine itself is concerned as well with populations and with the determinants of their health. The products of genetic engineering will appear as diagnostic reagents and as pharmaceuticals. Although they will be significantly useful in approaching individuals, they will have little utility in approaching the basic determinants of public health. The litany of the preconditions for health deserves repeating: pure water, hygienic disposal of human and animal wastes, pure foods in adequate variety and amount; decent housing, education and a background of political and economic stability are the essential preconditions for health. Neither diagnostic reagents nor elegant pharmaceuticals will substitute for their absence even though they may ameliorate the effects of such absence.

Occlusive arterial disease, in its many manifestations, may ultimately be better understood through the availability of analytic methods derived from genetic engineering. At the present time, however, it is not clear how this revolution in biology will directly affect this greatest cause of premature death in mature adults.

The abuse of alcohol, cigarettes and automobiles, along with outright homicide and suicide, constitute the most rapidly increasing causes of premature death among young adults. Although some amelioration of these destructive activities may be theoretically available through the use of yet to be defined psychoactive products of genetic engineering, it is, I believe, safe to say that the dynamics of the etiology of these destructive patterns is unlikely to be affected by such diagnostic or therapeutic agents.

The one great reservoir of death from infectious diseases that may be approached by this new technology is the realm of so-called tropical diseases. Where that disease is confined to humans or where humans are an essential link in the chain of the life cycle, it is theoretically possible that therapeutic agents or vaccines of such specificity and potency may be developed that the happy story of small-pox could conceivably be repeated. Much effort is being devoted to this possibility but the results are, at this time, so preliminary that it would be misleading to suggest that they are in any way predictable.

In my view, the greatest contribution of genetic engineering will be to strengthen the effectiveness of the phsyician in the traditional role of that profession. For each individual who is a patient, the possibility of early detection and specific disease prevention is brought closer to reality. With the availability of more specific diagnosis, the most appropriate therapy will become more readily identifiable. Anxieties about the presence of specific disease can be allayed with greater certainty and promptness. All in all, then, genetic engineering will contribute to the competence that is the ever-changing partner of the historic and unchanging compassion that motivates and characterises the physician.

When one recalls the state of affairs fifty years ago when infectious dis-

eases were still rampant, one would think that there would be a great general sense of satisfaction with the current state of affairs of health. As a matter of fact, the opposite may well be the actual case. My crystal ball would predict that even if all the potentials that have been suggested for the utility of genetic engineering in medicine are realised, by the time another 50 years has passed there will be as great concern about matters of health in that time as there is in the present – regardless of the differences that you and I might cherish.

Autoimmune disease

Professor Richard Batchelor
Royal Postgraduate Medical School

My task is to describe the technological prospects for the control and treatment of autoimmune disease as seen in the early 80s. It is not an easy assignment largely because of the complex nature of immune responses. I have therefore decided to concentrate attention on three issues. The first two are concerned with cellular and molecular events occuring in immune responses, and the last is how modern concepts affect our therapeutic and prophylactic approaches to the problems of autoimmune disease.

Cellular interactions in immune responses

Like any tissue, that of the immune system is composed of cells which have different functions. Broadly speaking they can be classified as T or B lymphocytes, and accessory cells. However, each of these classes can be further divided into sub-populations with differing functions, and characterised by possession of different cell surface macromolecules presumably related to their functions. Furthermore, organised lymphatic tissues have complex microanatomies which are relevant to the different cellular functions.

The first steps in a primary immune response are breakdown and phagocytosis of antigenic material which then is presented to lymphocytes. Depending on the characteristics of the antigen, B lymphocytes may respond directly, or the intervention of T lymphocytes may be required before B cells are triggered. These are known as T independent and T dependent responses respectively. T independent responses are invoked by substances such as polysaccharides in which each molecule displays repeated identical antigenic units (epitopes). The multiple epitopes are thought to favour high binding affinities with the B cells. T dependent antigens by contrast display one or only a few identical epitopes per molecule and fail to bind with sufficient affinity to activate B cells directly. As a result such antigens can only activate B cells indirectly, by intermediary cooperation or 'help' from T cells.

Virtually all the immune responses relevant to autoimmune diseases are T dependent and so no more will be said here on T independent responses. One more general point needs to be made, namely both B and T cells are genetically programmed early in differentiation to respond to specific antigenic epitopes, the response being to proliferate. Thus, individual antigens cause selective clonal proliferation as was first recognised by Burnett.

Antigen presentation

In T dependent responses, antigen is presented by specialised presenting cells to the T helper (TH) subpopulation of T lymphocytes. The identity of antigen presenting cells is the subject of current debate, but there is strong evidence in support of the notion that dendritic cells of lymphoid tissue and

Langerhans cells of skin belong to a common lineage which present antigen to TH cells. This process is incompletely understood but appears to involve the association of the antigen with the presenting cell's macromolecules of the major histocompatability system; I will return to this topic later. TH cells are only triggered into activity by antigen presented by the specialised presenting cell(s), free antigen being ineffective.

Activation of TH cells

Activation of TH cells leads to a number of consequences including

a) cooperation with B cells which in the presence of antigen differentiate into specific antibody producing cells;
b) mediation of delayed hypersensitivity;
c) stimulation of another T cell lineage to differentiate into cytotoxic T cells.

Cytotoxic T cells

During the past decade it has become clear that cytotoxic T cells (Tc) recognise their target, e.g. a virus infected cell, by interacting with *both* the virus antigens expressed on the infected cell's surface *and* also the major histocompatibility system macromolecules of the target cell. This and the fact that antigen recognition by TH cells also involves the same principle has led to the general concept that all T cells recognise antigen on another cell *only* in association with a self-recognition structure which is one of the gene products of the major histocompatibility system. Furthermore, different subpopulations of T lymphocytes use different histocompatibility gene products for recognition purposes.

Suppressor T cells (Ts)

T cells mediating antigen specific and non-specific suppression have been demonstrated in a number of experimental systems. Their mode of action is only partially understood and it would be inappropriate to discuss the details in this paper. However, there are good reasons for suspecting the Ts cells are important as modulators of immune responses, including autoimmune ones.

I hope enough has been said to convince you of the complexity of the interacting cell subpopulations, and that we should be seeking to learn the control mechanisms which ensure that the subpopulations operate in an integrated fashion.

How do T cells work?

There are two elements to be considered here, activation of T cells and how they mediate their effector functions. It has already been mentioned that in effect T lymphocytes 'see' altered self major histocompatibility macromolecules. The nature of the T cell receptors which combine with altered self and specific antigen is very uncertain. Because of the antigen specificity it has been proposed that *part* of the receptor is equivalent to the variable section of the heavy chain of immunoglobulin which contributes to the combining site of antibody. There is some experimental support for the proposition chiefly based on inhibition of T cell activation by specific anti-idiotype antibodies; but clearly T cell receptors have many differences

from serum immunoglobulin molecules. The molecular structure of the portion of the receptor which enables it to recognise altered self major histocompatibility molecules is also not known.

It does not need emphasising that a clear understanding of T cell receptors would be invaluable for the design of strategies to alter T cell interactions.

With the use of inbred animal strains it has been shown that immune responses are subject to genetic controls. Two independently segregating sets of genes relevant for discussion at this symposium have been identified – one set of genes belongs to the major histocompatibility system and the second is closely linked to the genes which code for immunoglobulin allotypes. Although precisely similar experiments cannot for ethical reasons be carried out in man, there is ample evidence that the same principles hold for man. Part of this evidence consists of the well known observations that all diseases in which immune processes make a substantial contribution to tissue damage show highly significant associations with specific HLA macromolecules.

Although the strength and character of immune responses are known to be influenced by an individual's HLA gene products, the mechanisms of this effect remain uncertain at present. Theoretical possibilities are legion, for example, variation in antigen association with presenting cells, or the repertoire of T cell responsiveness may depend on an individuals HLA phenotype; certain antigens may selectively activate suppressor T cell subpopulations according to the HLA antigens present and many other possible mechanisms can be imagined. However, presently available knowledge is consistent with the view that several different mechanisms are likely to be involved. Take for example the strong association between ankylosing spondylitis (AS) and HLA-B27 (90–95 per cent of AS cases are B27 positive, 5 per cent of unaffected white individuals are B27 positive). B27 belongs to the class 1 major histocompatibility system molecules, which are expressed on all nucleated cells and which are the self recognition units 'seen' by the subpopulation of T cells most of which have cytotoxic function. It is unlikely that the mechanisms by which B27 influences susceptibility to AS are the same as those involved in susceptibility to other diseases such as insulin dependent diabetes mellitus (IDDM), or rheumatoid arthritis in which the strongest associations appear to be with HLA-D region antigens, so called class 2 molecules, structurally different from the class 1 molecules and expressed only on certain nucleated cells. In addition, there are four genes within the HLA region of the 6th chromosome which code for proteins of the complement system, and there is growing evidence that they also are related to certain HLA/disease associations, notably IDDM and idiopathic systemic lupus erythematosus.

The second element in the question – how do T cells work? – is how they mediate their effector functions. As a result of development of methods to clone and grow T cells in vitro for indefinite periods, it has been possible to identify a series of T cell products which induce a variety of biological effects. Some of the T cell factors have antigen specific helper or suppressive activity, others are not antigen specific but enable specific subpopulations of cells to differentiate. The latter are now referred to as interleukins. Interleukin 2 (IL-2) is probably the best characterised and can serve as an

example. It has been purified to homogeneity; a monoclonal antibody against it has been raised. Although much remains to be learned about its biological action it is well established that IL-2 causes continuous proliferation of many T cell clones in vitro. It seems reasonable therefore to conclude that at least some T cells work by releasing factors which mediate specific biological effects on other cells.

Modern immunological concepts and autoimmunity

In general the natural history of most, if not all, autoimmune diseases appears to conform to the following pattern. Initially an environmental agent (which may be viral, bacterial, drug, or toxin) causes tissue damage. An immune response against self components released during the tissue damage ensues. The factors which control the character and persistence of this response are very incompletely understood, but one of them is the HLA genotype. There are certainly other controlling factors, some genetic and others non-genetic. But the important point is that we now have the means for identifying within a population those individuals who are particularly at risk of developing certain autoimmune diseases. In my view, the practical consequences of this will become increasingly important in medical practice.

A few examples will help to illustrate the potentialities. Insulin dependent diabetes mellitus (IDDM) is known to be highly associated with certain HLA genotypes. A recent epidemiological survey of Iceland (which has a population of approximately one quarter of a million people) led to the identification of a total of 266 patients with IDDM. Arnason and his colleagues have now typed 172 of them, and nearly 200 of their first degree relatives for HLA-A, B, C, and Factor B (Bf) of the alternative pathway of the complement system. This data has enabled them to genotype the majority of the patients and numerous unaffected controls. Five allelic combinations of HLA and Bf genes were associated with marked susceptibility to IDDM. If an individual received the high susceptibility combination from both parents the relative risk of developing IDDM was 60 (compared to individuals who lack the high susceptibility combinations). Gene combinations associated with low susceptibility were also identified, and individuals inheriting them from *both* parents had a relative risk of 0.12. These data show that in a population of this size and genetic homogeneity it is possible to determine with astonishing accuracy at birth whether a child stands a high, intermediate or low risk of developing IDDM during later life. With this information, environmental aetiologic factors can be more readily identified. In this context, strong suspicion has already fallen on infections during childhood with a number of pancreotropic viruses, for example, Coxsackie. Present evidence is consistent with the working hypothesis that such virus infections initiate damage to the islet cells, and that in individuals with high susceptibility genotypes persistent autoimmunity completes the destruction. If this hypothesis is correct prophylactic immunisation of highly susceptible children against the commoner pancreotropic viruses needs to be considered. Quite apart from humanitarian considerations, the economic effects of prevention or delaying the onset of IDDM by a decade or more would be so important that in my view a working group should be set up to look at the problem.

Another example of the value of detecting susceptible individuals is in the realm of immunologically mediated drug toxicity. It has been established that the development of the lupus syndrome after treatment with hydralazine (for essential hypertension) or nephropathy occuring in rheumatoid arthritis patients on gold therapy is significantly associated with the presence of particular HLA antigens. It is likely that more examples of this type will be found, and alternative therapies used for managing highly susceptible individuals.

Finally, I would like to draw attention to the importance of developments in isolating and characterising the various interleukins and other factors produced by mononuclear cells involved in immune responses. Already some laboratories are attempting to make probes for the genes which code for these factors, and there is a reasonable prospect that they will succeed now that it is possible to grow T cell clones in bulk and isolate their products with monoclonal antibodies. The exploitation of such factors in controlling immune responses is no longer an unreasonable concept, and one that is likely to revolutionise our management of autoimmunity.

To conclude I would summarise the position in the early 1980s as follows:

1 The immune response results from a complex series of interactions between functionally different mononuclear cells.
2 Control of these interactions is only partially understood; however, T cells recognise antigen in association with self major histocompatibility molecules ('altered self') and recognition is one control element.
3 Soluble factors synthesised by the interacting cells can mediate an array of functions likely to be relevant to their control and differentiation.
4 The ability to identify within populations those individuals at high risk of developing autoimmune diseases will grow in precision, and will be exploited more widely.
5 Advances in understanding of soluble factors synthesised by interacting immune cells will lead to their use in the control of immune responses.

Cancer chemotherapy

Dr Charles Myers
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My paper is organised into three parts. The first section deals with general comments about the old revolution in cancer treatment and what I see as the coming storm. The middle section is devoted to a specific example of where I think we are going. The final part contains some general comments about the strategies necessary for approaching the problem of the cancer cell.

Picking up Professor Teeling Smith's concept of two revolutions, I would say that the first revolution in cancer treatment was clearly the concept that chemotherapy could cure cancer. I think that now, 15 to 20 years later, the actual shock of that realisation has lessened somewhat, but I am not so young that I cannot remember, as a medical student, the first child that I saw with acute lymphocytic leukaemia who came in and rapidly went into complete remission. I remember seeing that patient five years later, and the shock that had for me personally. Most of us have either family members or friends who have had cancer, and as a disease it is one with tremendous emotional impact both for the physicians caring for the patients and for the people who have the disease and those who know the patient intimately.

In identifying the fruits of this first revolution we are now able to point to reasonably long lists of diseases which can be cured. To cure any disease – at least in internal medicine – is an unusual thing but with cancer chemotherapy we can now cure chorio carcinoma, acute lymphocytic leukaemia, Hodgkin's disease, testicular carcinoma, and certain patients with childhood malignancies such as Wilm's tumour, neuroblastoma and embryonal γ-abdomosarcoma. None of those diseases are common but they establish clearly the principle that cancer can be cured by drugs.

The progress to date in chemotherapy of cancer has largely been based on empirical usage of drugs; that is, a drug will be identified, often on the basis of empirical screening, to be active against a disease. It will then be combined with other drugs known to be active in that disease, and after a number of trials and adjustments the combinations will be found which will be curative. That has been the paradigm that has been used for the past 15 years. But for the past eight years and certainly for the past five years, it has become apparent to some of us that this paradigm has seen its day. That is not to diminish its accomplishments, but for many common cancers the empirical combinations are no longer generating improvements. For breast cancer it is now possible to compile a long list of drug combinations, including three, four or five drugs, all of which give comparable results without regard to the specific drugs put in the combination or the schedule in which they are used. The same situation holds for ovarian cancer, and I believe that we are reaching the same situation in cancer of the lung.

Many of us are asking: where next? I would have to say that in terms of Professor Teeling Smith's analogies the first revolution is drawing to a close and we are at the start of the new revolution, and at this point it is impos-

sible to see where that revolution is going or what all of its component parts are. I do, however, have some personal opinions.

Cancer treatment is one of great ferment at the present time, and I think, promise, but it is one of potential rather than concrete results – that is, the new revolution is forming. This ferment is fuelled by three developments. First, we now have a host of new biochemical techniques which allow us to understand our enemy, the cancer cell, in far greater detail. We now can take cancer cells out from patients and grow them *in vitro*, and study their biochemical properties and how they differ from normal cells, This development will be a key factor.

The second major factor has been the arrival of molecular biology and this is a leitmotiv which we will come back to again and again at this meeting. Molecular biology is extremely powerful. Its techniques are very elegant and will teach us a great deal. What they are helping us to do is define the process by which cancer cells become resistant to cancer drugs. It has taught us some very unusual concepts about the property of the cancer cell, for example, the fact that the tumour cell population is able to change its genetic composition under our very eyes as we pose it a therapeutic challenge.

Finally, something that is often overlooked, but is nevertheless true, is that chemists in general and drug chemists in particular, are now equipped with much more powerful tools than they were 15 years ago. This is reflected in the list of Nobel Laureates over the last 15 years by the number of advances in synthetic organic chemistry which have been so honoured. It is now possible for the drug chemists to tailor molecules in a way that they never could before. As biologists and biochemists we can now talk to them about our needs and have a reasonable hope that rather than providing us with analogues that are simply easy to prepare, they will be able to provide materials specifically designed for the biology of the problem in hand.

The revolution in cancer chemotherapy which will result from all this is complex and cannot be completely encompassed in this paper. I do believe, however, its essence can be stated very simply. We have now the realisation that the cancer cell population in a patient represents a very formidable adversary, and that we need to look at the moves this adversary is going to make in response to our therapies. We need to know in great biochemical detail what the range of moves and their frequencies will be and lay traps for the cancer cell in the direction in which it is going.

It is not possible in this paper to cover the whole field, so I will highlight a specific area in cancer drug research which shows clearly the historical antecedents which all revolutions have and which reveal the kind of strategic thinking which is taking place in our field, without claiming that this will be a success but just to give you a *gestalt* of what is going on.

The story I am going to relate really does have a historical antecedent and begins between 3000 to 4000 years before the birth of Christ when the Ancient Egyptians discovered that *Rubia tinctorum*, or the madder plant, has a coloured material in its roots which could be used to dye clothing. When that clothing was first immersed in either aluminum or iron salts and then immersed in the dye, the dye would then bind tightly to the cotton or wool fibre, forming a very stable bond. The colouring would survive multiple washing and exposure to sunlight. This became the classic dyeing tech-

nique in Ancient Egypt and spread throughout the Mediterranean basin, and even to the present day represents a classic method of dyeing. It has become known as the method of mordant or 'metal lake' dyeing. For example, in the Roman Legions the centurions' togas were dyed red by first dipping the cloth in alum and then in the extract of this plant root.

Turning to the chemical details, alizarin (Figure 1) is the dye material present in the madder root and it is dyed to the cloth by metal ion linkage. The transition metal ions such as iron and aluminum have a high affinity for oxygen, and what happens is that oxygen groups on the cotton fibre positioned with a certain spacing – about 2.65 angstroms – will bind tightly to iron. The alizarin dye also has oxygen atoms, again with a spacing of about 2.5 angstroms apart, which is perfect for forming a very tight metal ion bond between the dye and the cotton fibre.

How does this relate to cancer treatment and how does it relate to the broader world in general? The key structure in these mordant dyes is the quinone group with a hydroxy adjacent to it, either 1 or 1, 4 dihydroxy-quinones (Figure 2). I have outlined in black the groups that are essential for the chelate bond to form or the dye to form. On the right side I have a series of hydroxyquinones which are either effective anti-cancer drugs or toxic substances produced in nature. At the top we have adriamycin, which is one of our most effective anti-cancer drugs; it has a very broad spectrum of action and represents the best drug we have for a number of diseases. It is a member of the anthracyclines class of anti-cancer drugs, a group of great clinical and commercial interest. I think that well over 500 analogues of this have been synthesized by various drug companies in the search for a better adriamycin. The second on the right is juglone, a simpler structure. This is produced by the black walnut tree, which is native to North America. It has long been known that you could not grow plants such as tomatoes within the root zone of the black walnut tree and it is because this

FIGURE 1. **Details of how alizarin is bound to cloth by metal ions.** The portion in black is the metal binding site.

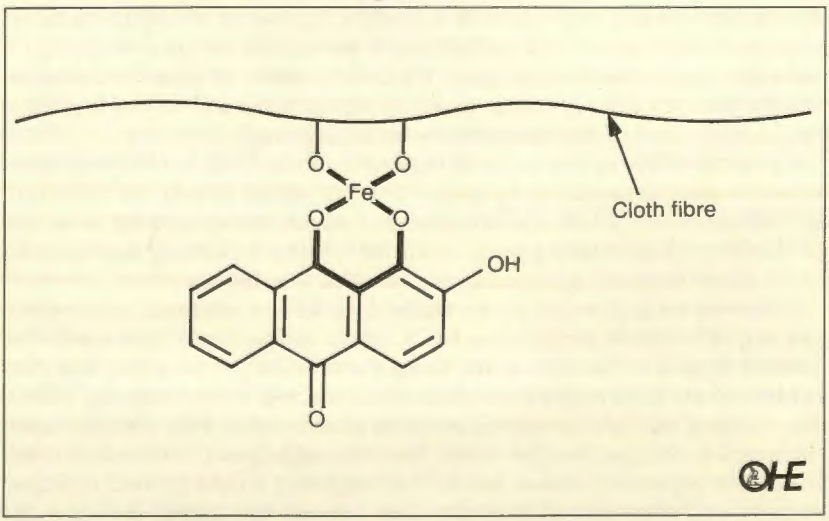
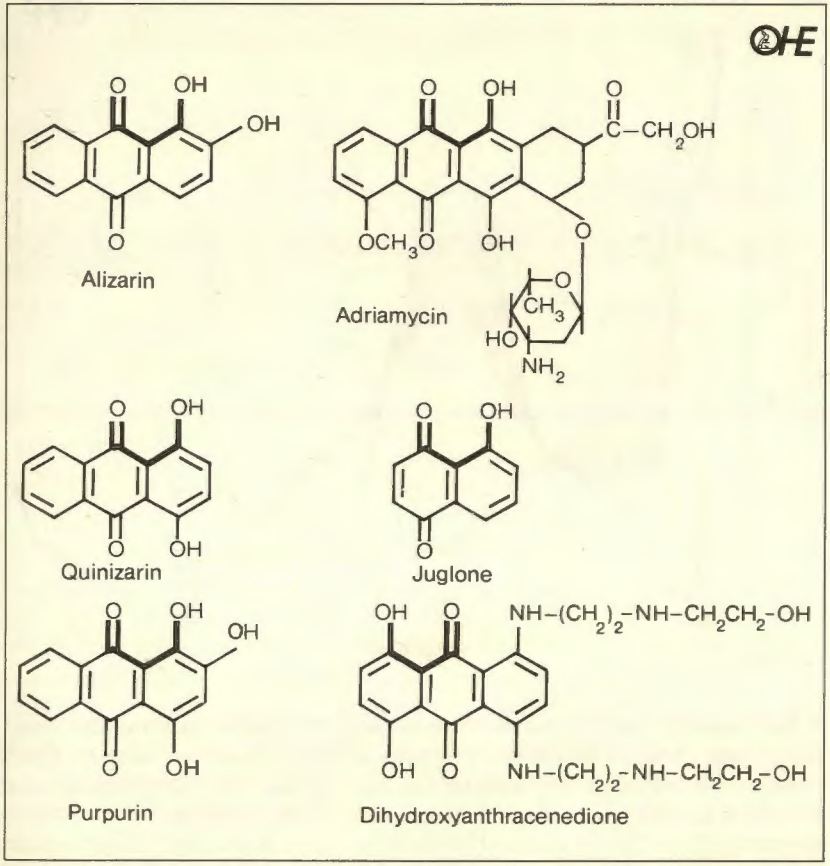


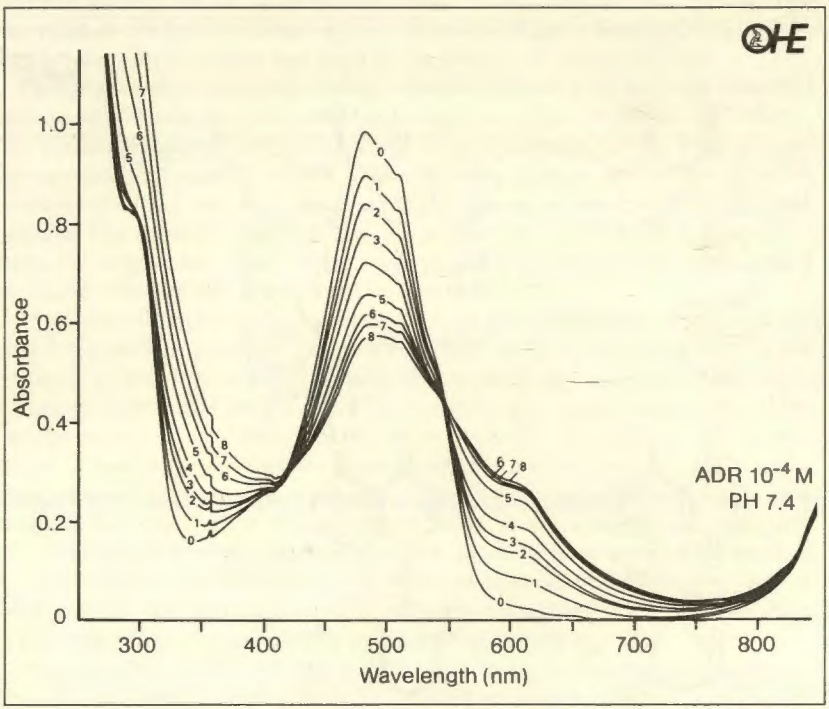
FIGURE 2. **A structural comparison between mordant or metal lake dyes and toxic quinones.** The portion in black is the probable metal binding site.



substance is secreted into the soil in the root zone of the plant. The American Indians used to take the immature leaves and fruits from this plant, mash them up and throw them into streams and use them to kill fish. The third on the right is dihydroxyanthracenedione, again an anti-cancer drug that has just come into clinical use. It is interesting that it is an active anti-cancer drug, as is adriamycin. It also appears to cause, in some low frequency, cardiac toxicity, as does adriamycin.

So, there is something about dihydroxyquinones which can cause toxic reactions and the structural analogy to the mordant dyes is quite suggestive. Figure 3 is a spectrometer tracing which simply quantitates the colour changes that I have described. Zero here represents adriamycin alone, which has a nice peak at 500 nm, and drops down to zero absorption at 600 nm. The addition of metal ion causes the disappearance of this peak and the appearance of what we call a charge transfer band in the 600 nm range. This occurs because there is extensive electron transfer between the drug and the metal ion.

FIGURE 3. **The absorption spectrum of adriamycin alone (0) or following addition of increasing amounts of iron (1–8).**

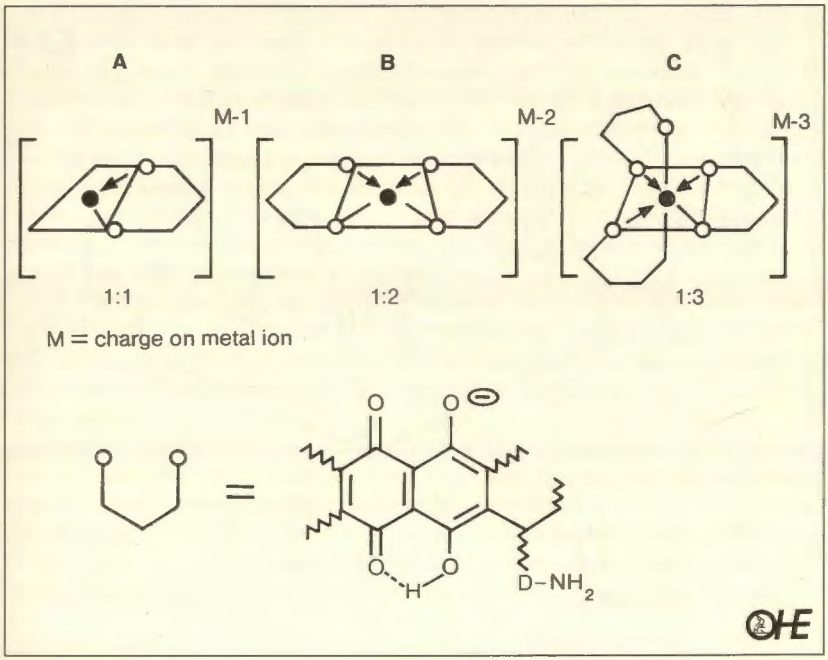


Subsequent to those observations we have been able to show the structure of the chelates which form (Figure 4). You can add as many as three adriamycins around a single metal ion and you can therefore have a 1:1, a 2:1 and a 3:1 complex where the metal ion is chelated by these adjacent oxygens.

Why should we be interested in this? I think at this point you have to know that the role of iron in cancer cell metabolism has been a source of considerable interest. This first started with the observation that radioactive gallium could be injected into patients and their tumours would light up: specifically in patients with oat-cell carcinoma and some of the lymphomas, the tumours would light up intensely with gallium III. It turns out that gallium III is essentially isomorphous with iron-III and that what we are really seeing is not gallium hunger on the part of the malignancies but the tremendous need that these tumours have for iron in order to grow. This has subsequently been confirmed by taking those specific cancer cells out, growing them in tissue culture and showing that iron is a growth requirement. For this reason we became very interested in drugs which might be activated by iron and how we could make use of that to design drug treatment strategies.

It then becomes important to talk more about iron and its biologic role. Iron overload, as you know, is a problem that is seen in some clinical situations, and research has been done on how to treat iron overdose or over-

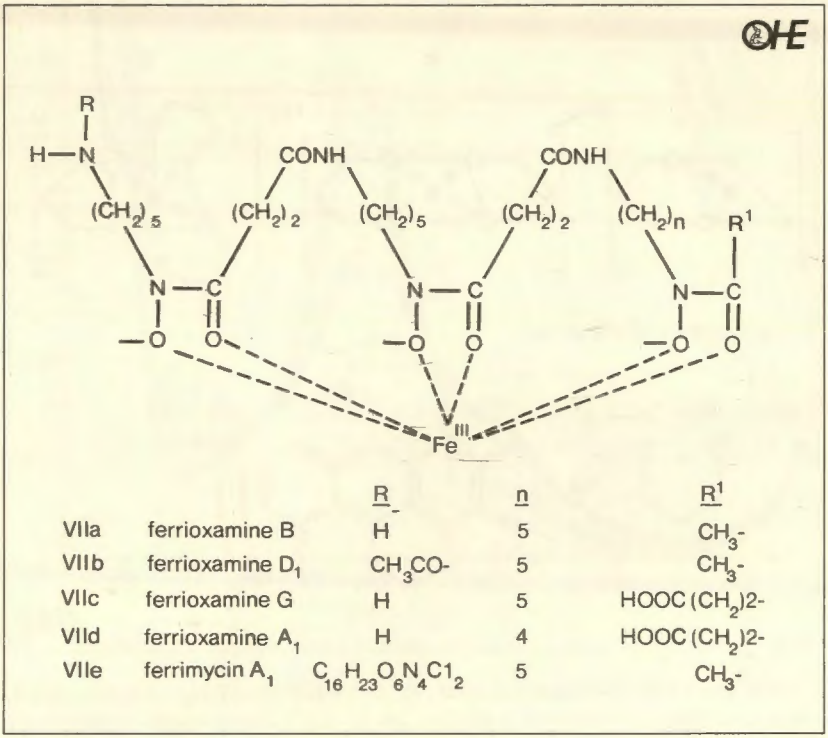
FIGURE 4. **Structure of the iron-adriamycin complexes.** A structural shorthand, defined at the bottom of the figure, is used to simplify the visual representation of the drug-metal ion complexes. The figure represents the 1:1 (A); 2:1 (B); 3:1 (C) complex



load. Some chelators have been developed which bind and remove iron in the body from the body. It is interesting to review what those compounds have in common with adriamycin, and what lessons we can learn.

The most effective of the iron chelators that are used clinically is desferrioxamine-B. The business end of desferrioxamine-B is three hydroxamic acid groups which bind the iron (Figure 5). Again, in analogy with adriamycin we have two adjacent oxygens. X-ray crystal structures have shown that the spacing between these two oxygens is identical in ferrioxamine-B and adriamycin. Actually it is slightly wider in adriamycin; theoretically, therefore, adriamycin would be perhaps a better iron chelator than the hydroxamic acids. In fact we have taken the published binding constants for adriamycin and acetohydroxamic acid and these are listed in Table 1. The point here is to show that there really is a very nice correlation between the affinity of acetohydroxamic acid and adriamycin for these various transition metal ions. This simply confirms the fundamental fact that the chelate environment, as far as the metal ion is concerned, is similar in adriamycin and in the monomer of desferrioxamine-B. This will be of great value to the drug chemist because it provides a quick way of predicting the affinity of the drugs like adriamycin for a whole variety of metal ions, and because the extensive information available on the geometry of iron chelation will allow drugs to be specifically altered either to increase the binding of iron or to alter its affinity for other transition metal ions.

FIGURE 5. **Structure of the ferrioxamine family of iron chelators.** Here, as with adriamycin and other hydroxyquinones, iron is bound to a combination of –OH and C = O groups. The distance between the adjacent oxygens here is nearly identical to that found in adriamycin



		R	n	R^1
VIIa	ferrioxamine B	H	5	CH_3-
VIIb	ferrioxamine D_1	CH_3CO-	5	CH_3-
VIIc	ferrioxamine G	H	5	HOOC $(CH_2)2$-
VIId	ferrioxamine A_1	H	4	HOOC $(CH_2)2$-
VIIe	ferrimycin A_1	$C_{16}H_{23}O_6N_4C1_2$	5	CH_3-

Adriamycin binds iron and copper and we understand something about the structure behind this. So what next? It turns out that the adriamycin iron complex and also the copper complex have a very interesting chemistry; that is, they act as a catalyst for a very important and potentially damaging reaction. GSH, or glutathione, is a very common substance in cells. It is a sulphur-containing tripeptide, and is the major mechanism by

TABLE 1 **Log of equilibrium constants for the formation of the 1:1 complex between adriamycin or acetohydroxamic acid and various metal ions.**

Metal Ion	Log K_{eq}(ADR)	Log K_{eq}(AHA)
Fe (II)	6.6	4.8
Mn (II)	7.0	4.0
Zn (II)	8.1	5.4
Cu (II)	12.7	7.9
Fe (III)	17.8	11.4

AHA = acetohydroxamic acid
ADR = adriamycin

which the cells prevent unrestrained oxidative reactions. You heard in Dr Vane's talk about how important oxidative reactions are for many normal processes. When out of control they can bring all sorts of problems, such as inappropriate prostaglandin production, destruction of cell membranes and cleavage of DNA. The adriamycin-iron complex has the potential to turn this system back on itself. Glutathione, instead of acting as a way of scavenging toxic oxidative species, actually acts as a source (Figure 6). Glutathione is able to donate an electron to the adriamycin-iron complex and this complex in turn takes molecular oxygen and reduces it to substances such as superoxide and hydrogen peroxide. What Figure 7 shows is the percent oxygen saturation in a solution versus time, in the presence of the adriamycin-iron complex, before and after the addition of glutathione, showing a tremendous acceleration in the disappearance of oxygen from the cuvette after the addition of glutathione.

I know that most of you are not chemists, but I do want you to understand the essence of this; that the adriamycin-iron complex has the potential to take a substance present in all cells for the purpose of preventing oxidative injury and to use this as a source for the production of damaging oxygen species.

The next question we asked ourselves – keep in mind, as Dr Vane said, that oxidative reactions can alter cell membranes and that the fatty acids present in cell membranes are susceptible to oxidative change. So we simply examined the ability of these substances to damage a membrane target; in this case, red cell ghosts (Table 2). We added adriamycin alone, iron, alone, iron plus glutathione, and did not observe damage. We then added

FIGURE 6. **Proposed biochemical pathway by which adriamycin-iron complexes can turn a normal defence mechanism back on itself.** NADPH is a common intracellular reducing agent which the enzyme glutathione reductase uses to reduce oxidised glutathione (GSSG) to reduced glutathione (GSH). Dox-Fe^R and Dox-FE^O represent respectively the reduced and oxidised adriamycin-iron chelate. O_2 represents molecular oxygen and O_2^- represents superoxide, the result of oxygen reduction. Superoxide, in turn, reacts to produce hydrogen peroxide and hydroxyl radical. The latter two are very damaging to mammalian cells

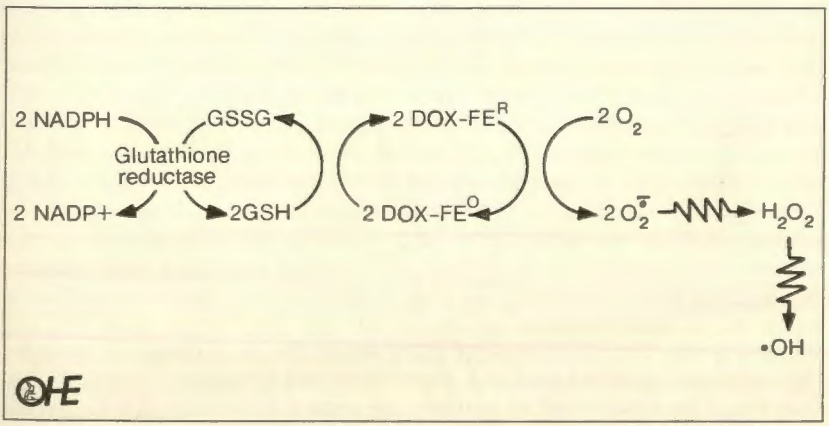
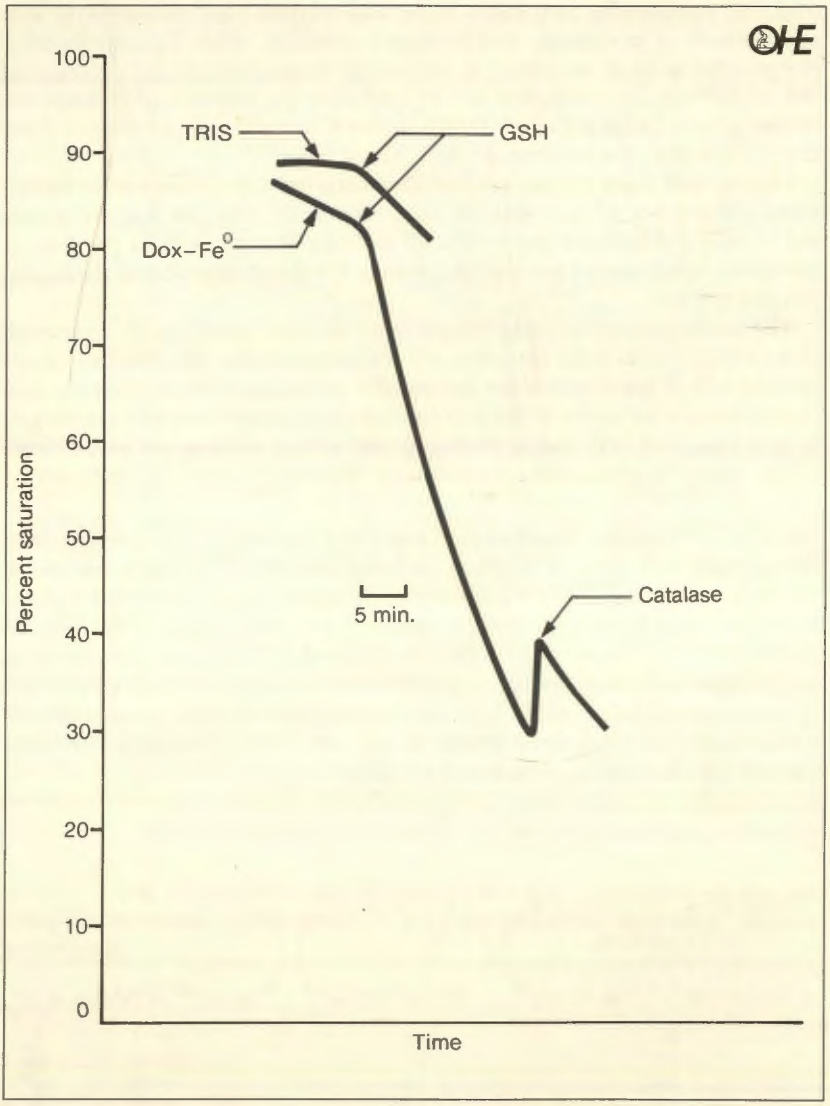


FIGURE 7. **Oxygen reduction by the adriamycin-iron complex.** The y axis shows the oxygen concentration as a percentage of that found dissolved in water at one atmosphere. Reduction of oxygen leads to a drop in its concentration. The graph shows the effects of various additions on oxygen concentration. Tris is a buffer in which all reactions are carried out. Addition of glutathione (GSH) to a solution of the complex (Dox-Fe°) results in rapid reduction of oxygen. This is the type of experiment used to study the chemical reactivity of the adriamycin-metal ion complexes



the metal ion drug complex alone and again saw no damage. If you take the metal ion complex and add glutathione you get nearly complete destruction. This destruction is partially prevented by superoxide dismutase

TABLE 2 **Damage to erythrocyte ghosts after 30-min contact time with iron complex*.**

Agents	% Intact Ghosts
Dox	100
Ferric ion	100
Ferric ion + glutathione	100
Acetohydroxamic acid complex	100
Acetohydroxamic acid complex + glutathione	100
Dox- + glutathione	100
Dox-Fe	75
Dox-Fe + glutathione	5
Dox-Fe ($FeCl_3$ as iron source) + glutathione	9
Dox-Fe + glutathione + SOD	65
Dox-Fe + glutathione + catalase	80
Dox-Fe + glutathione + SOD + catalase	100
Dox-Fe + glutathione + boiled SOD + catalase	5
Dox-Fe + glutathione + mannitol (10 mM)	50
Dox-Fe + glutathione + mannitol (50 mM)	50
Dox-Fe + glutathione + EDTA	100

* The concentrations used were doxorubicin (Dox), 0.1 mM; iron as the acetohydroxamic acid complex, 50 mM; glutathione, 15 mM; superoxide dismutase (SOD), 120 units/mL; catalase, 400 units/ml; EDTA, 1 mM.

Dox = adriamycin

Doxorubicin = adriamycin

which gets rid of superoxide, one of the oxygen species, and by catalase which gets rid of hydrogen peroxide, and if you combine the two you get complete protection. Thus, the two oxygen species produced were superoxide and hydrogen peroxide.

We knew that acetohydroxamic acid, which is the monomer of desferrioxamine, traps iron just the way adriamycin does and that its iron complex catalyses reduction of oxygen by glutathione. So as a control we ran the acetohydroxamic acid against an iron complex and glutathione and there was no damage. Here we have a paradox. These two iron complexes have fairly similar affinities for iron and are able to use glutathione to consume oxygen; yet one causes no damage to the red cell ghost while the other causes complete destruction, under very similar conditions. We were puzzled by this paradox, but in the process of doing the experiments we noticed that the red cell ghosts incubated in the presence of the complex became stained an intense purple colour, and we remembered that the mordant dye technique discussed earlier can lead organic molecules to be tightly bound to organic substances such as cotton, so we considered the possibility that the complex might bind to the red cell ghost. This proved easy to demonstrate and we were able to show that the adriamycin iron complex does bind very tightly to red cell ghost membranes. Adriamycin alone (here the name doxorubicin is used for adriamycin) itself binds to the red cell ghost membrane, but the metal ion complex binds much more avidly. It is essentially impossible to wash this metal complex off the red cell ghost. You can repeatedly centrifuge the red cell ghosts down in buffer and it will not come off. You can fragment the membrane with ultrasound and

again it will not come off. The only way really that we can quantitate this is through detergents which completely dissolve the membrane. Thus, the binding is essentially irreversible.

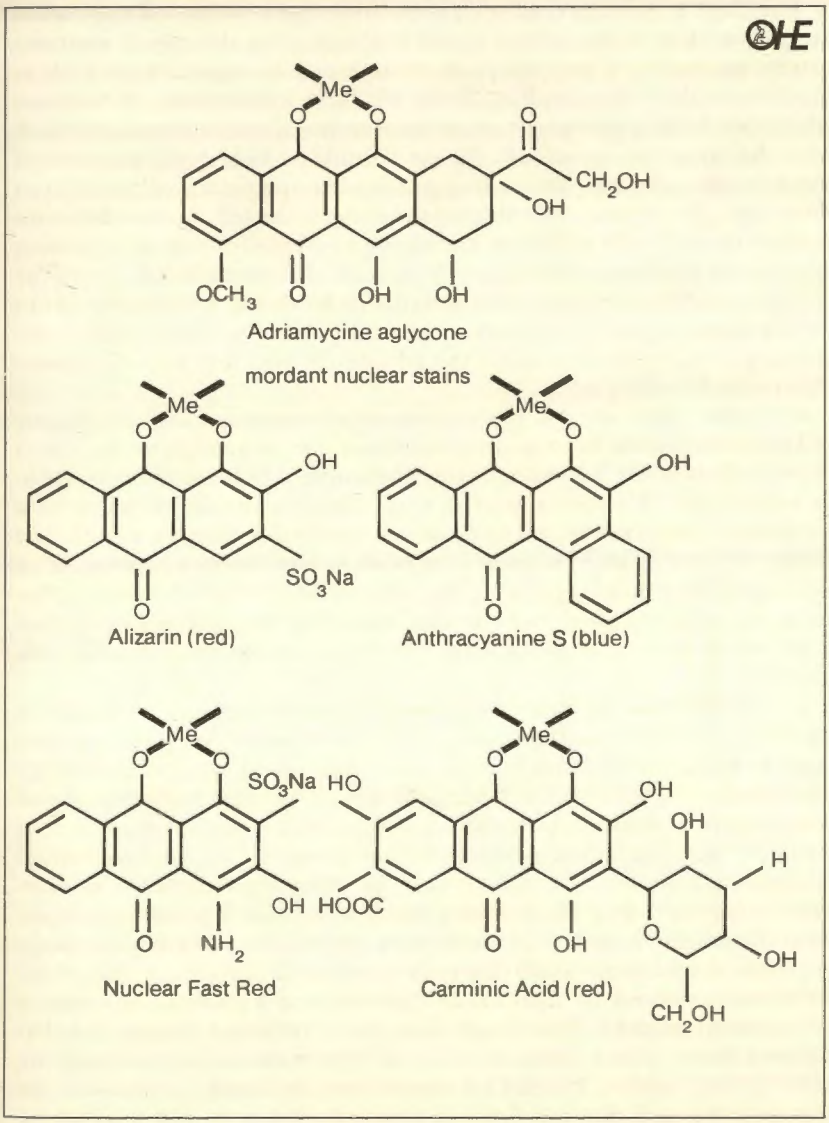
So the concept that we put together here is that the adriamycin-iron complex does damage to the red cell ghost because it combines two properties. The first property is that it is able to trap iron and catalyse reduction of oxygen by glutathione. The other property is that it is able to bind to a biologic target and localise the production of these damaging oxygen species right next to the surface of that target. This causes an enormous increase in efficiency.

Again going back to historical precedents, in the last century and the early part of this century considerable effort was put in by the dye chemists to create histochemical stains to stain various parts of the cell. One of the things that they were very interested in was specific nuclear stains. One of the most successful strategies for staining nuclei was first to take the tissue specimen and immerse it in iron or aluminum, and then transfer it into a solution containing various hydroxyquinones. Figure 8 shows the structure of a range of nuclear stains. Again alizarin, the same substance we started with initially, has been used as a specific nuclear stain. Anthracyanine-S, nuclear-fast red, carminic acid, which is the coloured substance in carmine, all bind to the nucleus and to the DNA in the nucleus via a metal chelate bond. All are also hydroxyquinones. Knowing this, we became interested in whether the adriamycin iron chelate would bind to DNA. Why do we want to know this? Because for a long time it has been known that not only does adriamycin bind to DNA but it also cleaves DNA *in vivo* and in tissue culture. The mechanism of this cleavage has never been satisfactorily explained, and it occurred to us that the chemistry we saw in the red cell ghost might offer a possible way out of this problem.

I will not go into the details but we have been easily able to show that the adriamycin-iron complex binds very tightly to DNA, and as with the red cell ghost membranes it is very difficult to get the complex off the DNA. For those of the audience who have worked with DNA, we must heat the DNA to 60°C in the presence of phenol in order to remove the adriamycin iron complex from the DNA. In addition we have been able to show that if the adriamycin iron complex bound to DNA is then placed in physiologic glutathione concentrations, DNA cleavage results. Thus, the drug-iron chelate is able to bind and damage cell membranes and DNA.

I told you specifically about the adriamycin iron complex. At this point what I have told you is of historical interest and some biochemical interest. I now want to step back and talk about how this might play into the strategic problems that I referred to earlier. First let me remind you of the biologic role that glutathione plays in a cell. As I mentioned, it helps protect against oxidative damage. One of the reasons it does so is that it is a substrate for the enzyme, glutathione peroxidase. This enzyme uses glutathione to reduce hydrogen peroxide to water. Clearly there is a gain there; hydrogen peroxide is more toxic than water – I think we would all agree with that. There are analogues of hydrogen peroxide which exist. These lipid peroxides are converted to lipid alcohols by glutathione peroxidase. The important point is that glutathione normally serves as a protective role in the cell. Another example of how glutathione gets involved in protecting

FIGURE 8. **The structural analogy between adriamycin and various dyes used to stain the cell nucleus.** The portion in black is the probable metal binding site



a cell is that many of the alkylating agents that we use are detoxified by glutathione. Alkylating agents were the first anti-cancer drugs and, indeed, are still the most useful anti-cancer drugs available and work by directly attacking DNA. It turns out that glutathione represents an alternate sacrificial target for alkylating agent attack thus sparing DNA, and that cells can get resistant to some alkylating agents by developing the capacity to produce more glutathione. The classic example of this is melphalan, one of the

most commonly used alkylating agents in cancer treatment. There resistance has been shown to depend on the development of high intercellular concentrations of glutathione.

Also there is another class of agents, cisplatinum, which is a very active anti-cancer drug. It has played a role in the curative therapy of testicular carcinoma, and it is very active in ovarian cancer. Again, thiols such as glutathione detoxify this drug. Thus, we have a substance, glutathione, which detoxifies a wide range of anti-cancer drugs, and tumour cells which have the capacity to genetically change themselves to be high producers of this substance. We now have a drug which will trap iron and potentially use those high glutathione concentrations to damage the cell. We can therefore present the cell with a difficult choice. By co-administrating an alkylating agent or cis-platinum and adriamycin to a cell that needs iron to grow, the cell faces the choice of increasing glutathione levels and getting resistant to the alkylating agent, but increasing its susceptibility to adriamycin; or decreasing its thiol levels to avoid the adriamycin trap and become susceptible to the alkylating agent.

Of course, there are still possibilities for the tumour. First, the tumour cell population could become independent of iron. It is not clear that this is biologically possible. Second, mutants could arise which are not permeable to adriamycin. This does appear to occur through the development of a membrane protein. We, in turn, would develop a counter to this last change by treating with cytotoxic antibodies against this new protein. All of this is very theoretical at present. The adriamycin-iron complex has not, for example, been shown to work *in vivo*. However, my main goal here has been to give you a flavour of what I think the successful approaches will look like.

Let me return to the concept of a Second Pharmacological Revolution in cancer treatment. I see the essence of this revolution being the sophisticated integration of therapy based upon knowledge of drug pharmacology and tumour cell biology. The latter is important because intelligent use of our drugs is dependent upon our knowledge of the biochemistry of drug resistance and population genetics of these changes. The concepts behind this approach are not new but it is only the recent breakthroughs in molecular biology and drug biochemistry which now make it possible to implement these ideas. In order for this to work, we will need to know the range of genetic mechanisms conferring resistance and the frequency with which these mutants occur. We next need to formulate well planned responses to the common mutants. This should allow us to formulate therapy like that outlined above, where common modes of drug resistance become unprofitable for the tumour. It could be argued that ultimately, given time, the tumour cell population can develop mutants resistant to any strategy we devise. The answer to that is not to give the tumour time. Restated another way, our strategy does not have to be perfect, it only has to be good enough that given the initial tumour population size and time to the death of the last cancer cell resistance does not have a chance to develop.

There is good evidence that this can be done. I suspect we have empirically achieved this effect in the use of combination chemotherapy in Hodgkin's disease and testicular carcinoma. In addition, this is the reason that advanced tuberculosis is successfully treated with combination drug

therapy but not with successive single agents. The difference is that now we may be in a position to formalise this approach through skilled use of specific knowledge about the drug-tumour cell interaction.

Finally, the concepts may provide a cognitive framework in which to combine chemotherapy, radiation therapy and surgery. The latter is of value in that it provides a means of reducing the size of the tumour cell population and thus the probability of resistant mutants arising. Radiation therapy shares similar chemistry and biochemistry to several commonly used cancer drugs and should, in principle, be approachable in the same way. These prospects are very exciting and, I think, offer real promise for major advances in the treatment of cancer.

Discussants

PROFESSOR SUNE BERGSTRÖM
Karolinska Institute, Stockholm

Following this morning's presentations, I should like to make a few observations of a general nature. The first concerns the problem of the population explosion taking place in many of the developing countries of the world. In this context the research on prostaglandins described by Dr Vane may in fact offer a potential means of controlling this growth.

Prostaglandins can interrupt pregnancy at any stage of its duration; alternatively they can be employed to start labour at full term. During the studies that we were involved in with the World Health Organisation it was found that abortion induced in any period from the fourth or fifth week onwards often resulted in incomplete abortion, requiring 'clinical clearing up' and thus hospital care. The completely unexpected finding, however, was that during the first three weeks after the menstrual period abortion is practically complete. This finding offers the possibility that prostaglandin suppositaries could be made available to women for self-administration when they find themselves to be over time. Perhaps this method of birth control, which appears to have no deleterious sequelae for the one third of women who are over time but turn out not to be pregnant, will spread over the next decade to the developing countries. It is a quite unexpected development in this field.

Another point I want to stress is the enormous capacity that exists for research efforts to come to grips with new leads and problems. The burst of research activity, reflected in the annual count of journal and other publications, which followed Dr Vane's aspirin discovery is indicative of the potential that exists for advancing the frontiers of knowledge. In this context I also want to draw attention to the valuable role that the pharmaceutical industry can play in expediting such progress. Thus companies can help, for example, by making samples available to university research departments for experimental work – as did the Upjohn company with their prostaglandins. Industry's role will remain the same in many fields: in molecular biology, for instance, university and industry research are now working closely together.

Thirdly, it requires emphasis that the current health situation in the developing countries is a major problem that is adding to the inequality and instability in the world. In such nations up to 50 per cent of persons dying are less than 5 years old. The remaining deaths are distributed throughout the age spectrum. By sharp contrast, mortality in modern Western Societies such as Sweden is predominantly clustered among the older age groupings. Yet 200 years ago Sweden's mortality profile was reminiscent of the pattern demonstrated by today's developing countries. The major contemporary problem is that two thirds of the world's population have yet to achieve this demographic transition. For this reason the last 10 years have witnessed a significant escalation of research activity aimed at resolving this problem.

This is reflected in the increased economic support for such investigations. The total budget of the World Health Organisation is little more than

$200 million a year, but during this year special research programmes for human reproduction, tropical diseases and viral diseases have obtained voluntary support from member states which is approaching $60 million. This is now a research council of international dimensions.

The interesting thing is that this organisation is absolutely similar to any research council modelled after the British Medical Research Council. It has scientific working groups for each specific area (for example, malaria chemotherapy, malaria immunology, malaria field trials) consisting of something like eight to twelve of the leading experts in each field who decide how the money should be spent. WHO staff fulfil only a secretariat type of function. The important point is that at the top there are thirty national government representatives and the majority are from developing countries. This is in effect a scientific subcommittee for tropical diseases of the World Health Assembly. It is completely different from the usual UN bureaucratic system.

Apart from the project side there is also a research strengthening group that is building up at strategically located places in developing countries clinical and other research facilities. Such local arrangements have emerged as a valuable source of very good and rapid clinical data. Generally it is very difficult to perform clinical trials in developing countries, many of them do not have drug regulatory agencies and they are reliant on the World Health Organisation for assurance and control.

The activities I have described are on a relatively small scale compared with the $6 or $8 billion spent on medical research in the industrialised world, although they have stimulated a lot of additional activity in the latter. But this is by no means the only problem for the developing world: in a few decades there will be many more aged people in these countries than in the industrialised world. In Sri Lanka, for example, the rapid fall in the death rate is combining with a high birth rate to generate a 2 to 3 per cent annual increase in population. In Sweden, on the other hand, reductions in death rates have been matched by changes in birth rates such that a position of balance has now been achieved.

Listening to this morning's papers I suspect that some members of the audience, such as the economists, may have experienced difficulties in fully understanding all of the technical details that were presented to them. Nevertheless, I believe that the ability to predict disease remarked upon by Professor Batchelor might have an important bearing on future developments. If we could diagnose the constitution in early childhood we might be able to predict appropriate behaviour patterns for an individual which would increase his or her chances of remaining healthy. We might also be able to develop the means of predicting mental development and thus perhaps the roles individuals might fulfil in society. Whatever the medical and sociological developments, I believe we are going to live through a continuous revolution.

PROFESSOR RONALD GIRDWOOD

Edinburgh University

It is a long time now since Professor Teeling Smith surprised and flattered me by suggesting that I might be able to be one of those introducing the

discussion after four technical papers, outside my own field of experience, had been presented to a distinguished audience. I must admit that I had doubts about the wisdom of agreeing, but, since I retire from my University post exactly a week today, forty-eight years after I started as a medical student, I thought that it would be a challenge to find out whether I was still able to appreciate just what is going on after having spent so much of my time on clinical duties and committee work. I am sorry if it makes you feel like guinea pigs, but I think it may be useful to illustrate the problems that a clinician faces in attempting to keep up to date.

Dr Hubbard has referred to the state of affairs fifty years ago when infectious diseases were still rampant. My father, a pharmacist, died of tuberculosis in 1933. Obviously I have witnessed the changes in disease patterns and in medical practice in the Western world throughout almost all of these years, but I also travel sufficiently widely to know about the continuing problems of the developing countries.

I have two photographs taken when Professor A J Clark, the head of our Department of Pharmacology, was giving us a lecture in 1936 on the treatment of infection. On one board he has written 'fomentations, lavage, bacteriostasis'. He then turns round and writes on another board the word 'Prontosil' and can be seen consulting his notes as he writes the formula of sulphanilamide. Probably none of us realised it, but here was a major turning point in the history of our ability to give potent therapeutic agents.

In some ways we are now at another, less dramatic, turning point nearly fifty years later because of our much greater detailed knowledge and as a result of the development of laboratory and manufacturing techniques that nobody could have foreseen. We are a step beyond the development of new drugs by more or less standard techniques, and one difficulty is that the subject matter has become so specialised that in some instances almost a series of new languages has to be learned if there is to be any attempt at understanding. For example, the term plasmid has been used this morning, and in May of this year there was a four page coloured insert in various medical journals with helpful diagrams about genetic engineering in relation to the production of insulin, something clinicians should now know about. It stated that a gene for a desired protein can be produced by chemically synthesising DNA from a known base, or by copying back to DNA from a messenger RNA. There follows the information that the gene is introduced into a host cell via plasmids, described as 'rings of DNA which are extracted from bacterial cells'. As most of you will know, the plasmid is cleaved chemically so that the gene can be inserted, and closure is effected by means of a ligating enzyme. This recombined plasmid is then introduced into a host cell and inside it the reprogrammed plasmids resume replication. The accompanying diagrams in this helpful article put out by a pharmaceutical company show the divided cells with the plasmids at one end and the chromosomes at the other.

The trouble about this is that those who have written the account for the edification of the general medical reader, like many others, assume that he will know what a plasmid is, to a greater extent than that it is merely a ring of DNA. The fact is that most of the clinicians who study the diagrams lack this necessary basic knowledge, and cannot understand why a plasmid, if it conveys genetic information, does not become part of a chromosome. I

asked twenty-two medical colleagues, ranging from house physician to consultant, and only one knew about plasmids, this being because he had read the *New Scientist*. With one or two there was frank disbelief at the suggestion that there could be extrachromosomal self-replicating elements in a cell. In addition, I consulted eight British and two American textbooks used by medical students and only one gave information about plasmids. Obviously, as our knowledge is augmented almost logarithmically and as new terms have to be coined as a result, most medical graduates find it increasingly difficult to follow what is being described in the literature or even at medical meetings. To know, without understanding, is not satisfactory. I found therapeutics a difficult subject as a medical student. The treatment then available was largely empirical or traditional and did not make sense. Now it is becoming too difficult to understand.

I have had the pleasure of visiting a manufacturing plant where genetic engineering is being applied in the formation of medical products and I was very much impressed by the way in which biologists, chemists, engineers and others have dealt with the tremendous problem of converting the alteration of a cellular structure, using reprogrammed plasmids, into a large scale industrial process. I am assured that *E. coli* K12 or other organisms that may be used will not be converted into epidemic pathogens or induce serious changes in micro-organisms in the body or elsewhere.

Reference has, of course, been made this morning to the production and use of monoclonal antibodies. Here we have a technique for producing antibodies of a desired specificity and immunoglobulin isotype. In summary, from the practical point of view, which is what interests me, monoclonal antibodies can be used to eliminate T cells (which cause graft versus host disease) in donor bone marrow, both in myeloid leukaemia and in aplastic anaemia, and to make renal transplantation more successful. Monoclonal antibodies directed against cancer cells and malaria parasites have been developed and, as has been said, others have been used to purify interferon. I understand that the possibility of immunological contraception is being explored. I note, too, and am interested in the idea, that a very toxic agent such as ricin or perhaps diphtheria toxin may be attached to a monoclonal antibody and carried direct to target cells, or perhaps a radioactive substance can be carried. Professor Batchelor has referred to the use of monoclonal antibodies to isolate products of T cell clones, but, when I read elsewhere about hybridomas which develop monoclonal antibodies against other monoclonal antibodies, I was confused. I am glad that he has explained to us the complex activities of the T cells, as this is something which I myself had to summarise a few months ago and found to be hard going. We are again faced with a complex subject and new names, such as interleukins. It was most interesting to learn about the survey in Iceland and the theory that virus infections may damage the islet cells; it is to be hoped that some benefit accrues from these observations: this seems likely.

So far as interferon is concerned, I do not know how true it is, but I have read that the annual world production is about 1 gm., and that it costs about £50 for a trillionth of a gram, but the cost is likely to fall. I know that it can be produced by fibroblasts, leukocytes or lymphoblastoid cells derived from a Burkitt lymphoma, while gamma interferon, which has not yet been purified to the extent of the alpha and beta forms, can be induced

in T lymphocytes by mitogens or antigens. I realise that many interferons are species specific, but I wonder whether there is any prospect of obtaining a non-species specific form that is produced in animals but acts on humans. Some interferons, I know, are too toxic for clinical use, and, so far as I am aware, almost all the material that has been employed in the treatment of humans, so far, is of the alpha type. Perhaps, by genetic engineering, DNA sequences, capable of programming for the production of human interferons, may be inserted into micro-organisms, and I understand that a likely method of adding to our supplies is by direct cloning of organisms that produce alpha interferon, the starting point being human leukocytes induced to make interferon by Sendai virus. I know that at least eight distinct genes code for different human alpha interferon molecules and that the implications of this are not yet clear. The therapeutic value of interferons in viral infections and in human malignancy has not yet been established, although recent unwise press publicity has raised false hopes in many households.

The work of Dr Vane and his colleagues on prostaglandins is well known to all of us. The possible therapeutic applications of our new knowledge in relation to thrombosis is what interests me most, and it is clear that the substances being considered are:

(a) prostacyclin analogues infused intravenously;

(b) thromboxane synthetase inhibitors such as UK-37, 248-01;

(c) selective antagonists of thromboxane.

Related to our knowledge of thromboxane A_2 and of prostacyclin, it remains to be seen whether aspirin, either alone or with dipyridamole, will have any real ability to prevent secondary myocardial infarction. I must admit to having more faith in the value of giving β-adrenergic blocking agents after a myocardial infarct. As for the information about leukotrienes, this sounds most exciting and important, but is new to me today so I am in no position to make helpful comments.

At one time I had considerable experience of the results of treating malignant disease with the early therapeutic agents and there were some remarkable and long continued beneficial effects, in conditions such as chronic lymphatic leukaemia. Now, however, our knowledge of the classification of the diseases, particularly the leukaemias and lymphomas, is so much greater and the programmes of drug therapy frequently so complex that management is usually better carried out in specialist centres. I do think, however, that sufficient is known about the value or otherwise of splenectomy for this operation to be carried out less often that it is in some treatment centres. Perhaps the best we can do for our individual patients is to have fed into a computer all that is known about these conditions, including the detailed histology, and also computerise the results of the many clinical trials that have been carried out with different drug programmes. From this data bank the best choice of therapy for any individual could perhaps be obtained, provided the information was constantly updated.

We have come a long way in our knowledge of medical treatment since I became an undergraduate in 1934, but at the OHE symposium held in this College in 1978 on the subject of 'Medicines for the Year 2000', Dr George Paget had to report that he had been unable to obtain sufficient replies to a

questionnaire about possible future developments to merit their analysis. No doubt the matters being discussed today and tomorrow are giving us a good indication of possible developments, but what I am sure we must certainly expect in the future is the totally unexpected.

GENERAL DISCUSSION

The main papers presented to the second session of the symposium demonstrated very clearly, in spite of the highly complex nature of the subject matter, that understanding of the functioning of internal systems and of disease processes is progressing at a rapid pace and offers extremely bright prospects for valuable therapeutic advance. Against this background of great optimism, Dr B. B. Newbould (ICI plc) commenced the general discussion by asking the speakers to identify any potential problems which might serve to constrain the momentum of current research activity. This theme came to dominate the entire discussion period.

Consideration was inevitably given to the question of the resources available for funding research and, disturbingly, it was noted that there was already evidence of financial pressures in the university sector. Thus Professor Girdwood revealed that insufficient funds meant that the vacancy shortly to be created by his retirement would remain unfilled. Dr Vane indicated that he, in common probably with other research directors in the pharmaceutical industry, was receiving a growing number of requests for financial help from university researchers. There is no denying that valuable pharmacological advance has stemmed from collaboration between the industry and academia in the past and will continue to do so in the future. However, Dr Vane expressed concern that university research should be seen to be independent and academic and that an undue extension of industry support might inhibit these desirable qualities by placing greater emphasis on applied investigation. Introducing an international dimension, Professor Bergstrom drew attention to the limited funds available for research into tropical diseases.

Focusing the discussion more specifically, Dr Hubbard suggested that, from United States experience, clinical research was under particular threat. He noted not only decreasing opportunities for young people to obtain simultaneous qualifications in a basic science discipline as well as a clinical discipline but also a rapid decline in the opportunities for clinicians with an investigative frame of reference to their clinical work. Such developments potentially constitute a major obstacle to the Second Pharmacological Revolution because of the crucial significance of the final stage of clinical evaluation in the development of new medicines.

Dr Myers drew attention to the problems of conducting clinical trials in cancer research and in particular to the difficulties in obtaining conclusive results. The latter clearly emphasises the need for high standards of training for individuals engaged in such work but this requirement would not appear to be facilitated by the developments in clinical research noted by earlier contributors to the discussion. On a more optimistic note, Dr Myers indicated that in the United States at least, sufficient monies are available for the funding of cancer research.

Professor Batchelor made the general comment that one of the conse-

quences of inadequate levels of finance in the UK has been the enforcement of continued reliance on 'eighteenth century management techniques . . . in looking after patients and running laboratories.' In particular he argued that the compilation of accurate records and their subsequent analysis – the essence of clinical research – would be greatly facilitated by the use of microcomputers. Yet the resources for such investment are severely constrained and, furthermore, attempts to equip medical students with skills in this area have not been encouraged sufficiently.

Moving away from these more general research issues, Professor Batchelor also responded to a member of the audience who had asked whether any other work was in progress, besides that already described, on the association between HLA and drug toxicity. In this context he referred to a paper in press dealing with the industrial disease of scleroderma induced by vinyl chloride. He pointed out that while many people experience relatively trivial symptoms, a few individuals are affected severely and that there is evidence to suggest that the latter group have an unusually high frequency of one of the HLA antigens. Professor Batchelor concluded that there are several drugs where it might be worth mounting research programmes to look for HLA linked toxic side effects.

SESSION III

THE ECONOMIC CHALLENGE

Chairman: The Lord Vaizey

The subject to be considered in this third session of the symposium is the economic challenge facing the pharmaceutical industry as it embarks upon the Second Pharmacological Revolution. As a means of commencing the proceedings I should like to issue three brief challenges.

It seems to me that the pressures for expenditure on health care are now pressing against the ceilings of relatively stagnant national incomes. This presents a particular challenge in that the therapeutic possibilities may very well rapidly exceed the economic feasibility and this will generate all sorts of economic, social, scientific and political consequences.

Secondly, the expense of basic research has risen steadily and is now enormous. The era of major yet low cost scientific breakthroughs – we are all familiar with stories such as that of Rutherford and his cocoa tins and bits of string – is quite clearly far behind us now.

Finally, and perhaps most important, the cost of development from basic research through to usable product has now exceeded any previously foreseen possibility. This is particularly so in the case of the pharmaceutical industry and has arisen principally because of the public's desire to pursue absolute safety. Yet such a goal is not achievable in any sphere of human endeavour.

It seems to me, therefore, that there exists a very real set of economic problems which hangs over the future of the Second Pharmacological Revolution.

Europe: the economic challenge

Otto Nowotny
F Hoffmann–La Roche & Co Ltd, Switzerland

While *the technological prospects* for a second pharmacological revolution during the next two decades are truly formidable, *the economic challenge* of putting these prospects into practice is equally formidable.

It was the Danish philosopher Kierkegaard who once said that *between knowing and doing lie all the excuses.* What's the use of spending time and money on *knowing* what we can do, if in practice we are unable – or not allowed – to *do* it?

And by 'we' I mean without presumption and hesitation the research-based pharmaceutical industry. This belittles in no way the numerous past, present and future contributions from the universities, national and international organisations, and individual researchers outside the industry. It just means that to translate the results of worldwide pharmaceutical research into safe, efficacious, high-quality medicines available in the required quantities at reasonable prices, necessitates numerous well-run industrial firms of international dimensions with *sufficient funds* at their disposal.

The availability of these *funds* is closely linked to a variety of *factors* – some positive, some negative – which, of course, exert their influence not only in Europe. But let it be said right away: Western Europe's economic well-being depends to a far greater degree on its pharmaceutical industry than does that of the United States and of Japan. Western Europe's drug industry employs nearly 400,000 people, ie, over twice as many as that of the United States and nearly four times as many as that of Japan. And Europe's drug exports exceed its imports by over $3 billion, which is more that twice the favourable drug trade balance of the United States and – with inverted signs – over six times the pharmaceutical trade deficit of Japan.

Europe, as Professor Teeling Smith's historical perspective has shown us, can rightly be considered the cradle of modern medicines, with roots extending nearly two thousand years into the past. It will now be up to the governments of Western Europe to show some foresight – to grasp the importance of the various favourable and unfavourable factors, which in the next two decades can easily make or break one of Europe's leading industries – and to start acting accordingly. And contrary to the Sunday preacher who when preparing his sermon wrote in the margin 'weak point – shout!', I want to whisper to our European politicians: 'This may be your last chance.' And when I say that, let me add, I am not *Japanicking.*

Amongst the major factors influencing the development of the pharmaceutical industry and constituting the economic challenge Europe has to face in the coming decades I want to limit myself to a mere dozen, namely six *positive* and six *negative* factors.

Starting with the positive factors, I want first to discuss the role of **population growth**. Of course, more people – if they are to be adequately supplied – means an increased demand for medicines and this will have a

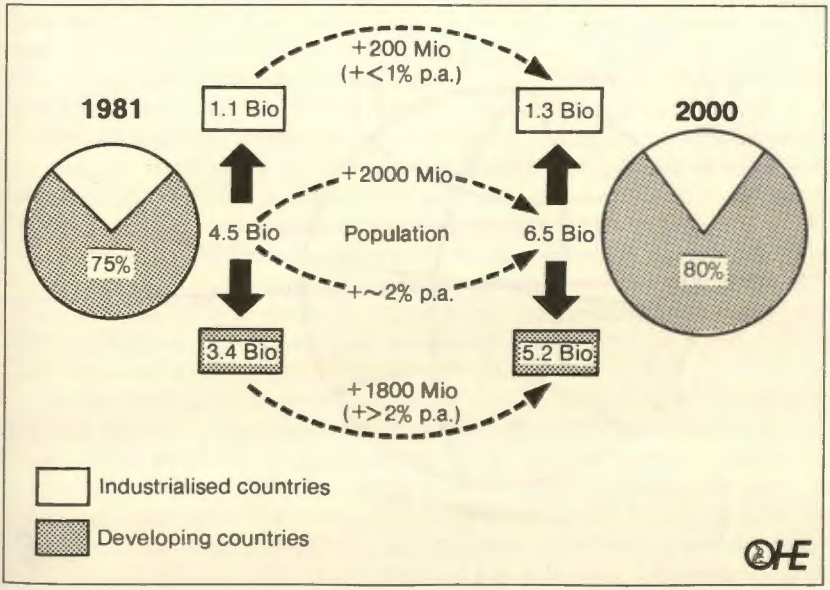
stimulating effect on the pharmaceutical industry in the coming decades. However, one has to differentiate immediately between the *industrialised* countries, where the average population growth is likely to be *less than 1 per cent per annum* during the next two decades, thereby increasing today's population from about 1.1 billion to 1.3 billion in the year 2000, and the *developing* countries, where growth is *over 2 per cent per annum*, thus raising today's population of 3.4 billion to 5.2 billion at the end of the century (Figure 1). In other words, today's developing countries will increase their share of the world population, from around 75 per cent today, to 80 per cent in the year 2000. Or to put it in absolute terms: from the additional 2,000 million people who will be living on this earth at the end of the century, only 200 million – or 10 per cent of the total increase – will be accounted for by today's industrialised countries but 1,800 million – or nine times more – by today's developing countries.

To supply 2 billion more people with medicines will necessarily require an increase in production by the pharmaceutical industry. But in order to satisfy the needs of these growing populations the pharmaceutical industry's product range will have to be adapted to the requirements of the Third World.

This will not be an easy task. Because 10 to 20 years usually elapse between starting research on a specific compound and introducing it as a safe, efficacious quality medicine at a reasonable price, important decisions have to be made by the managers in pharmaceutical companies *today*, in the hope of seeing the results of these decisions during the last decade of this century.

A *second* positive factor is the **increased access to drugs**. Here again we have to differentiate between the *industrialised* and the *developing* countries.

FIGURE 1 **World population**



While most of the industrialised countries can probably claim that well over 80 per cent of their populations have access to all the drugs they need, most of the developing countries can equally well say that over 80 per cent of their people do *not* have access to the drugs they require.

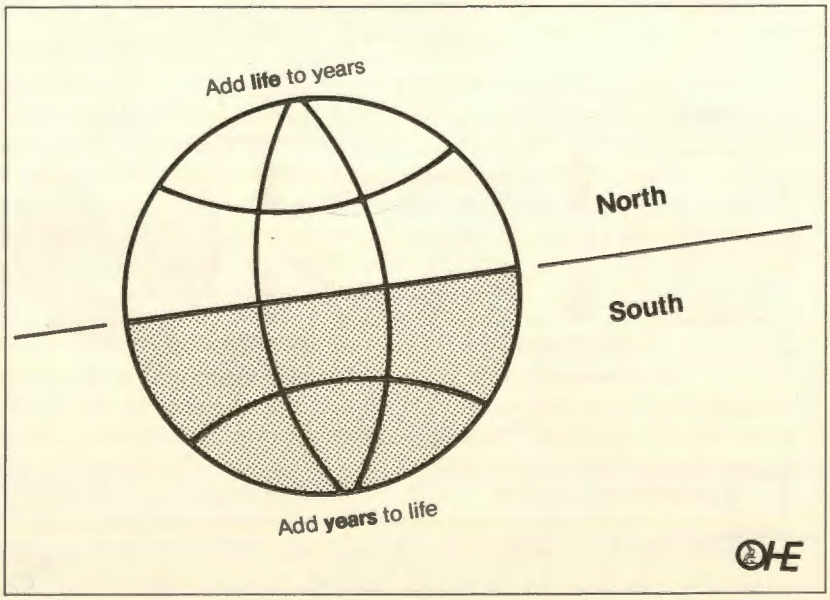
Thus, apart from the nine times steeper increase in the populations of developing countries during the next two decades, the serious lag in access to drugs is a second, powerful stimulus emanating from the Third World to increase the production of medicines. But to meet the resulting demand will not be a simple matter, partly because of absence of the infrastructure necessary to assure adequate distribution, partly, however, because of simple lack of funds.

A *third* factor likely to create more demand for medicines is the general trend towards **increased longevity**. Contrary to what science-fiction minded people might like to believe, I think we must accept for the time being that the upper limit of the individual human life span on earth is around 100 years. Yet, even such a realistic assumption still implies that today's average life span could be lengthened enormously by about one-third in the industrialised countries and just about doubled in the developing countries.

Of course, increased longevity by itself is not a sensible goal if the increase in the quantity of life is not accompanied by an increase in its quality. And while the so-called South may for the foreseeable future still have to try to 'add years to life', the more fortunate North is already giving considerable thought on how to 'add life to years' (Figure 2). This, by the way, is the very motto the WHO chose to mark its most recent World Health Day on 7 April of this year.

A *fourth* positive factor lies, of course, in the development of **better**

FIGURE 2 **Health care priorities**



drugs. Some critics of the pharmaceutical industry dismiss the majority of new drugs disdainfully as mere molecular manipulations worth neither the money nor the time involved. But these critics fail to recognise how slow *all* human progress really is!

To illustrate this point I don't want to limit myself to the somewhat extreme example of Aristarchos of Samos, the Greek who discovered three centuries before Christ that the earth revolves around the sun, and not vice versa, and who would have had to live an additional 1,900 years in order to see his truth finally vindicated by Copernicus.

Consider, for instance, a product all of us are most familiar with, the motor-car! How long did it take to get the diesel engine widely accepted, and when were the first cars equipped with front-wheel drive, which nowadays more and more producers seem to look upon as the state-of-the-art solution? Do we really find *major* improvements whenever we change our cars?

Thus we shouldn't be surprised that progress in pharmaceuticals too is mostly a *step-by-step* affair in which the differences between existing drugs and their successors are not as apparent as we (the non-specialists) would like them to be. It is only with the passing of time that we begin to realise that slight improvements here and there have finally constituted an important step forward. Discrediting of *minor* progress ultimately stops *all* progress! We must be realistic. Even small changes in the formulation of drugs can be desirable improvements and make it easier for patients to comply with their doctor's prescriptions, speeding up their recovery and thereby saving on costs.

I want now to consider the *fifth* positive factor – the dream of every drug company researcher and manager – **the breakthrough drugs**. As the term implies, we cannot expect such discoveries to be frequent. Sir Henry Hinchliffe put it very clearly way back in 1958 in his report on the 'Cost of Prescribing' to the British Minister of Health: 'It may be reasonably asked how much research is necessary before a valuable new drug is discovered. This is a difficult question to answer. Really outstanding drugs are still very few in number and if a firm makes one major advance in 10–20 years it is doing very well'. What Sir Henry wrote 24 years ago is still valid today!

And while breakthrough drugs will help individual drug manufacturers to increase their research efforts substantially, the growth in sales and profits which these exceptional drugs generate would always turn out to be rather modest if spread over the whole pharmaceutical industry. After all, the main prizes in the state lottery, if distributed evenly amongst all the ticket-holders, wouldn't amount to very much either. Thus, the willingness of *many to lose a little* in the hope of *once* being amongst the *few to win a lot* is as powerful a motivator for those who invest in the lottery as it is for those who run the risks of pharmaceutical research.

On the basis of these facts I would say to all politicians and health-care officials who are responsible for setting the legal and administrative framework within which the drug industry has to operate: 'Whenever you are in doubt about the practical consequences of your decisions, be sure to replace in your mind the research-based pharmaceutical manufacturer by the man in the street out to buy a ticket in your state lottery, and ask yourself if the conditions you have established are such that a maximum num-

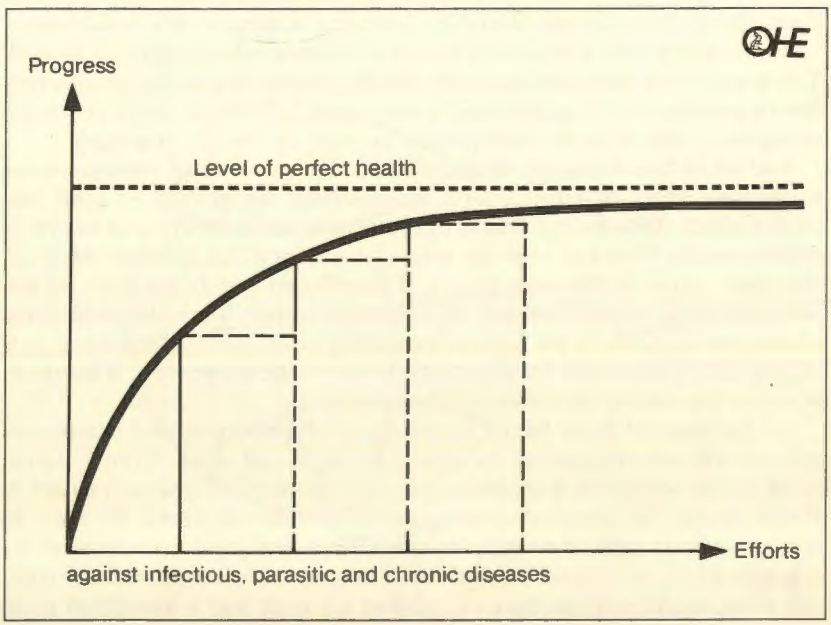
ber of people will want to participate. If your answer is *yes*, you're on the right track. If the answer is *no*, you'd better go back and do your homework!'

As the *sixth* and last positive factor influencing the development of the pharmaceutical industry I would like to mention the evolution of **new technologies**. The latter, such as genetic engineering and biotechnology, will, to quote a recent British white paper on 'Biotechnology' – 'be of key importance to the world in the next century, and of rapidly growing importance before then'. These new technologies may well ring in a second pharmacological revolution, especially in conjunction with the rapid progress made by computers, which are now moving towards the new horizon of *artificial intelligence*. The 'dumb' computer, like so many other products and industries, is likely to be transformed rather quickly into a relic of the past.

Turning now to the negative factors there is first of all the **rising cost of research**. This phenomenon may be called the 'Law of diminishing returns' or the 'Law of Pareto'. Let us forget all these economic labels and just remember that in every field of human endeavour the more progress we want, the greater the effort we have to make. You'll be a pretty mediocre piano player if you practice your instrument for less than one hour a day. To impress your listeners you might have to devote at least two hours a day to it, and to become a top concert pianist six to eight hours of practice per day may be absolutely necessary.

Pharmaceutical research faces the same problem as we extend our research from the infectious to the parasitic and on to the chronic diseases (Figure 3). To find one new active substance that meets the accepted standards of drug safety, efficacy, quality and price may take anywhere from eight

FIGURE 3 **Rising cost of research**



to ten years and cost 50 to 100 million dollars. The rising cost of research is a trend which is unlikely to be reversed. The new technologies I have mentioned may well bring substantial savings in energy and production costs, but to develop these technologies – to cite the British white paper again – 'may require research-funding mechanisms beyond those at present available'. Yet, somehow, these funds will just have to be generated!

A *second* negative factor concerns the **delays in registration** which are particularly costly for the pharmaceutical industry, where the time necessary for discovering and testing a new drug is becoming increasingly longer. Efforts are now being made by various registration authorities such as the American Food and Drug Administration to shorten these delays, but it remains to be seen whether a major improvement of a durable nature can be achieved.

A *third* negative factor is the **weakening of patent protection**. There is a rather widespread view, particularly in developing countries, that patent protection is just a device of the rich to 'fleece' the poor countries, and that in abolishing or simply ignoring patent protection, drugs can easily be obtained at a lower price. If this attitude persists, it will, I fear, soon turn out to have been a very costly error.

The same reasoning is applied in the case of the *fourth* negative factor of **abolishing brand names** and replacing them with generic names. It seems very difficult to convince people that patents and brand names are not devices for unreasonable exploitation but a temporary and partial protection necessary to motivate increasingly risky and costly pharmaceutical research. Unfortunately, there are also some industrialised countries, such as Canada with its compulsory licence laws, which do not shy away from hanging on to the coat-tails of other nations and getting a free ride on drug research. The hypocrisy of such an approach becomes strikingly evident if one just thinks where international drug research would be if all other nations were to act in a similar way!

A *fifth* negative factor is the various governmental **volume controls**. In eliminating or restricting the reimbursement of certain drugs by national health insurance, in narrowing their use and reducing the size of the pack dispensed or the number of repeat-prescriptions, health-care authorities are often trying to limit their drug reimbursement expenditures by reducing the volume of medicines consumed. The drug industry is, of course, *not* interested in seeing its products used in unreasonable quantities, for the simple reason that such overuse of its medicines would certainly be detrimental to the health of the patients and thereby to the industry's long-term health as well. Thus, in many instances the industry has cooperated with the health insurance funds in motivating patients to adopt a more reasonable attitude in their use of medicines.

A recent example of this approach is a leaflet which has been devised by a group of health insurance funds in the French-speaking part of Switzerland in cooperation with several pharmaceutical companies, and which is now being distributed by these funds to their patients in Switzerland (Figure 4). I think such a leaflet might have sent shudders down the spines of some hard-boiled pharmaceutical marketing men a decade or two ago. Today it is indicative of the enlightened self-interest international drug companies find more and more acceptable.

FIGURE 4 **Medicines: a dear friend!**

You can avoid overconsumption and wastage of medicines:

- Don't measure the quality of your doctor by the length of his prescription!
- Don't insist on his always prescribing more, and something new.
- Don't stop treatment simply 'because you feel better'.
- Follow scrupulously the instructions of your doctor and your pharmacist.

The *sixth* and last of the negative factors I have on my list is, I fear, one of the most serious for the development of the research-based pharmaceutical industry and constitutes its major economic challenge. It can be summed up with the term **price controls**.

These are particularly pernicious in times of steep inflation such as the last decade. Inflation rates of 10 to 20 per cent, as are found even in many industrialised countries, cannot be neutralised by mere rationalisation and/or increases in volume if price adjustments are officially limited to less than half this percentage.

I don't want to labour this point, but if we want to explore the very exciting possibilities drugs can still offer us in the coming decades, the positive factors can only influence the development of the pharmaceutical industry if the negative factors are kept to a minimum.

As can be seen in Figure 5 from all the factors I have dealt with, numbers (1) to (3) demand that we succeed in those areas shown under (4) to (6). And to do so, the negative influences of factors (7) to (12) will have to be minimised.

Although it is difficult to make a reliable projection as to how factors (1) to (6) are going to influence the world drug consumption in the next two decades, it is probably not unreasonable to assume that the share of less than 20 per cent of all drugs at present consumed in the developing countries (making up about 75 per cent of the world population) may have

FIGURE 5 **Major factors influencing the development of the Pharmaceutical Industry**

Positive factors	Negative factors
1 Increased population	**7** Rising cost of research
2 Increased access to drugs	**8** Delays in registration
3 Increased longevity	**9** Weakening of patent protection
4 Better drugs	**10** Abolishing brand names
5 Breakthrough drugs	**11** Volume controls
6 New technologies	**12** Price controls

increased to about 40 per cent of the total by the year 2000 (when 80 per cent of the world population will be living in those same countries). With world drug consumption likely to rise by about 150 per cent by the end of this century, you can see the overall growth of around 5 per cent per annum will – under the assumptions I have made – be composed of a roughly 3 per cent increase in the industrialised countries and a percentage increase nearly three times as high in the developing world (Figure 6). Also in absolute terms the increase in drug consumption in the industrialised countries should be at least equalled, or even surpassed, by the expected increase in the Third World.

To conclude my remarks and to put, at the same time, things into their proper perspective, let me say that we – I mean the research-based pharmaceutical industry – are not so naive as to believe that the vicious circle of poverty, destruction of the environment, and disease can be broken just by more and better drugs or by more and better health care. The WHO's very ambitious goal of 'Health for all by the year 2000' will make it necessary to deal with major problems in a considerable number of other important areas, often long before drugs, doctors and hospitals can come into full play and make their contribution to human health (Figure 7).

Thus, I do not have to stress to you that, ideally, problem areas (1) to (10) should all be largely dealt with before or at the same time as problem area (11) – as they usually are in the industrialised countries. If direct health care in developing countries is nevertheless given more priority than it would logically deserve, this is simply because expenditure in all the other problem areas is so much higher if visible results are to be achieved as soon as possible. Thus it costs only a few dollars *per capita* to vaccinate all children world-wide against the six most prevalent childhood diseases. But it costs a hundred times as much to improve the supplies of safe drinking water, to

FIGURE 6 **World drug consumption**

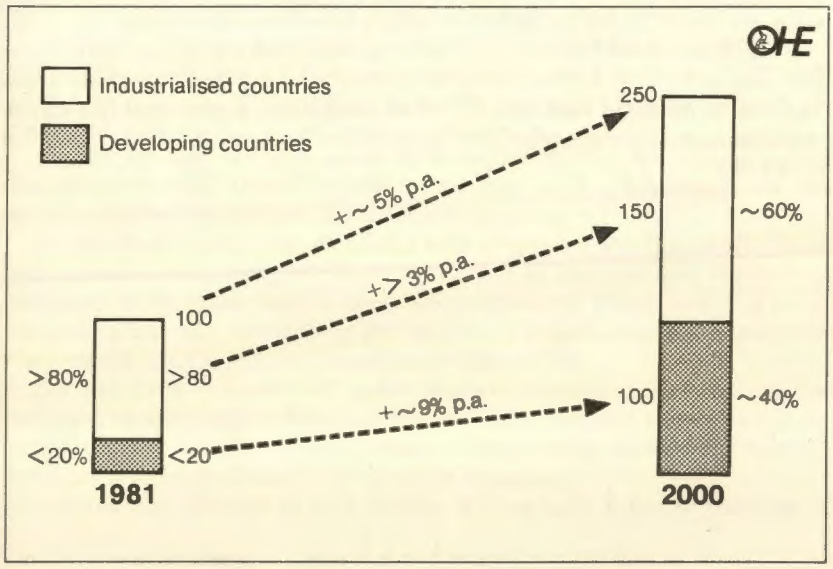
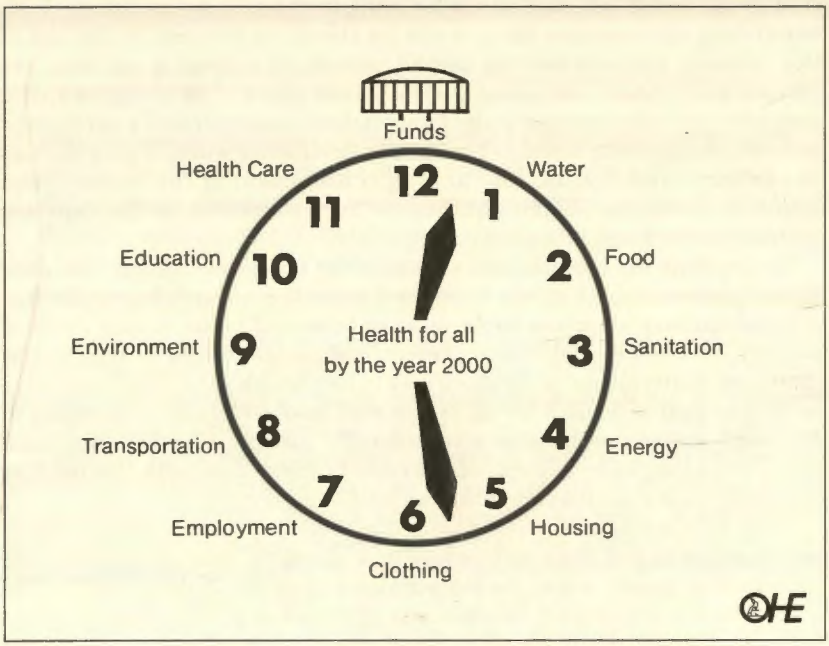


FIGURE 7 **Health for all by the year 2000**



install proper sanitation, to create adequate housing, education, etc. This is why problem area (12) – *adequate funding* – is finally so important.

The general shortage of funds, exacerbated by the present economic difficulties in most developing and industrialised countries, is in no way helping governments to face the continued rise in health-care costs from a long-term perspective. Yet mere administrative controls to obtain health-care costs are bound to fail in the future as they have done in the past.

To the world-wide health care cost dilemma there is, in the end, one – but only one – answer: Providing the proper environment for **major innovations in medical care** and for **more enlightened personal life styles**. And *that is*, as all people who have stopped smoking know, *all very simple, but it isn't easy*!

The United States: the economic challenge

Lewis Engman*
Pharmaceutical Manufacturers Association, USA

When I first looked at the agenda for today's meeting, it was plain to me that, of the two principal topics to be discussed, I had been assigned the easier. The earlier speakers were being asked to predict the medical significance of the Second Pharmacological Revolution. I had only to accept the developments they forecast and to project the probable economic consequences.

I don't think there can be any question that the Second Pharmacological Revolution will produce huge benefits – in the form of both lower costs for health care and simultaneous improvements in its quality.

Some of these economic benefits will be direct: there will be savings as cheaper drug therapies are substituted for more expensive forms of intervention. The need for surgery will be reduced. As will the need for hospitalisation.

Substitution of more effective drug therapies for those currently on the market will produce other direct savings. Diseases that today require prolonged drug therapy may in the future be cured with shorter and surer courses of treatment. Better still, some diseases may be prevented. The productivity of physicians will increase as their arsenal of weapons becomes more sophisticated. And lives will be saved.

There will also be indirect benefits: labour productivity will increase as the percentage of the labour force idled by ill health declines. Industrial costs, and therefore prices, may reflect reductions in disability payments to employees who without the new medicines would be unable to work.

Finally, there will be savings of the sort it is impossible to measure – reductions in pain and suffering, lessening of the burdens borne by families of the bed-ridden, the liberation of those who bear these burdens to re-enter the work force and lead productive lives.

Economists may disagree about their magnitude but there should be no disagreement that these benefits will occur as a consequence of the pharmaceutical innovations discussed this morning.

To this the historical record speaks with eloquence. One could fill a book with statistics describing the savings realised in the past fifty years from advances in vaccines, sulpha drugs and antibiotics. These earlier innovations have not only saved countless billions of dollars, they have rewritten the demographic profiles of countries the world over.

But history is not our only guide. Future economic benefits from the Second Pharmacological Revolution also can be inferred from what every economist knows to be the very nature of innovation: namely that societal savings are a precondition for innovation's success.

For any new product to be a success, it must offer more or cost less. It

**In his absence, Mr Engman's paper was read by Mr Frank Fowlkes.*

must in other words, confer on those who buy it and on society at large – whose labours and resources are accordingly re-allocated – a net social gain. Positive economic consequences are not, therefore, the measure of an innovation's success: they are its cause.

Having offered this happy forecast, let me hasten to warn you that while the potential benefits of new pharmaceutical innovations are nearly certain, the expeditious emergence of these innovations as new products is far less certain. The breakthroughs that compose what we are calling the Second Pharmacological Revolution are, in the main, still in the conceptual stages.

New conceptual breakthroughs are stimulating. Important new conceptual breakthroughs are also exciting. People convene conferences and symposia to discuss them. But no one has ever been cured by a new concept. For a new concept to become a cure, someone must convert it into a new product or a new process. I need hardly remind this audience that the benefits of penicillin, for example, were well understood long before anyone knew how to make penicillin available at a price that would permit its general use.

In the pharmaceutical industry today, the leap from concept to practical application requires large investments and considerable risk. It is estimated that, in the United States, the average cost of bringing a new product to market is in excess of $70 million. For each new compound that becomes a new product, 9,999 compounds are discarded along the way.

Investments and risk-taking on this scale require a business environment that is relatively predictable and a regulatory philosophy which respects the fact that investments are made only where investors have a chance to recover costs plus a reasonable return for taking the risk.

Today, world-wide trends threaten to increase the costs of pharmaceutical investment while at the same time reducing the likelihood those investments can be recovered. In many countries, governments are flirting with regulatory policies that extend well beyond questions of safety and efficacy, policies that would significantly alter the economics of drug research and that almost certainly will slow the pace at which the concepts discussed this morning become the products we hope to see tomorrow.

One expects this in state-managed economies. State-managed economies have pursued such policies for years. Their record of new drug development sadly reflects it. But such policies are now being advocated in countries – my own included – where, heretofore, governments have shown respect for the vitality of the free market.

Advocates of these new economic regulations apparently have become so accustomed to the steady march of science that they take it for granted. They seem to assume that intellectual curiosity is by itself sufficient to power the innovative process. They seem to view the corporation that finances innovation, not as a vital participant in the process, but as merely the exploiter of its fruits. They ignore the fact that without the corporate risk-taker, most new theories would never evolve beyond scribblings in a copybook, that most new medicines would never leave the laboratory bench. And so today we see proposals for stricter price controls, for profit limitations, for restrictive formularies and for reductions in patent protection.

Such proposals arise in part because nearly every country in the world today shares two problems: one is the rapidly rising cost of health-care brought about by increased factor costs, by the near-universal prevalence of third-party payment programmes and by the rising demands of populations to whom medical science offers a larger-than-ever array of products and services. The second problem is chronic budget stringency.

To the government faced with these two problems, drug expenditures present an inviting target. Compared to other components of the health-care system, drug expenditures are relatively easy to control. To the politician striving to cut costs, drug expenditures appear to be one place where he can demonstrate devotion to fiscal responsibility while minimising his risk at the polls.

Though drugs demonstrably save more than they cost, the tendency of politicians to make drug firms scapegoats for general cost and budgetary problems may get worse before it gets better.

If the breakthroughs promised by the Second Pharmacological Revolution are successfully brought to market, one effect could be to increase the percentage of the national health-care dollar spent on drugs.

New drugs will displace other forms of therapy such as surgery because they are cheaper and/or more effective. There will be a net savings to society. But as drugs assume a larger fraction of the therapeutic burden, it is probable that they will also account for a larger fraction of health-care spending. A reasonable man would count this substitution and the associated savings as progress. But as I have already suggested, reason for the moment seems to be in short supply. As new drug innovations enter the market, it is possible that we could see the saddest of ironies: a new generation of therapies retarded by its very success.

A cycle in which new products lead to increased drug expenditures, which lead to politically inspired regulatory reaction, which leads to a slowdown in the rate of new product introductions is one I devoutly hope we can avert. But we may not avert it unless the public and the public's representatives can be made to see the folly of the regulatory prescriptions currently being offered.

Let me, therefore, take a moment to discuss three varieties of regulatory intervention that seem to me most ill advised.

The first is price controls. The assumption underlying price controls is that returns to producers exceed the level required to ensure that producers will continue to invest and produce at current rates, and that these excess returns may be skimmed off without affecting either rates of investment or levels of supply. The assumption is that prices are, in a word, 'uncompetitive'.

This manifestly is not true in the case of our industry. There are literally hundreds of drug firms selling in nearly every major market in the world. There are on the market in most countries more than 2,000 different products, and new ones being introduced every year. The competition between these firms and products is illustrated by the behaviour of drug prices.

Drug prices have, for more than a decade, been rising much more slowly than prices of nearly everything else consumers buy. Even though drugs have been taking over a larger and larger share of the therapeutic burden,

expenditure on them has been declining steadily as a percentage of health-care spending.

In a state-managed economy it may be possible to control prices without affecting short-term investment or supply; the state can mandate investments and levels of production, though by doing so it will pay a high price in the form of reduced investment and supply in other sectors.

In war-time it is possible to control prices with few short-term ill effects, because the government can appeal to patriotic instincts by asking firms to suspend considerations of economic self-interest. But in a free economy, in peace-time, price controls can have only one effect. That is to reduce current supply and to reduce the investment that will determine future supply. This has been proven over and over again.

The second regulation I want to mention is the restrictive formulary. Advocates of the restrictive formulary would limit market access to relatively few products – those they deem most useful. They argue that many products simply duplicate others, that some products are better than others and that it is wasteful for the consumer, or the consumer's doctor, to have to deal with a confusing array of choices.

Now, countries with scarce resources may find virtue in the formulary approach – at least with respect to drugs purchased with public funds. Certainly every country has the right to impose a formulary if it chooses. But those who so choose should be aware that there are costs associated with the formulary approach. And that these costs may be quite significant.

To begin with, different people react differently to any given drug. What is best for most people may not be best for all people. So there is value in variety. But an equally significant effect of a formulary or any regulation that restricts market access, is to increase the risks, and therefore the costs, of new drug development. These are considerations advocates of the formulary approach ought to ponder.

The third regulatory proposal I think worth mentioning is the suggestion that patent protection for drug products be reduced – or, where patent life already has been reduced, that restoration of lost patent life not be permitted.

Those who advocate reduced patent protection argue that the public interest is best served by permitting generic competition at the earliest possible date. This is extremely short-sighted. Strong patent protection is vital to continued drug innovation throughout the economy. In my country, where drug patent life has been cut in half by lengthening approval times, we have seen innovation decline. In Canada, where compulsory licensing has rendered the patent system a nullity, we have seen drug research and innovation all but cease. To what end? No good purpose is served by any measure that reduces the rate of innovation.

The consumer has every right to demand competitive prices. But the competition that most effectively reduces prices is the competition provided by new and better products. Nothing drives down the price of a good, old drug as fast, or as far, as the emergence of a better new drug. Nothing ensures the rapid reduction of that new drug's price so effectively as the pressure it puts on competitors to discover a drug that is newer still and better yet.

Strong patent protection is essential to ensure that this most salubrious

of all forms of competition is vigorous. Strong patent protection ensures one other thing advocates of patent reduction conveniently overlook: it ensures that none of us will have to wait for better therapies that might have existed had the importance of patents been adequately appreciated. Which is the most important benefit of all.

What these three ill-advised regulatory proposals add up to is a general rejection of the lesson that free-market forces are the best and most efficient protector of the consumer's interest.

Nowhere has this lesson been more eloquently expressed than by Dr Sanjaya Lall of Oxford University in a speech delivered last June in Washington. At one time an outspoken advocate of strict industry controls and regulation, Dr Lall appeared that day as a convert. His text was the woeful experience of India, a country that decided some years ago to impose stringent controls and regulations and that today finds its pharmaceutical resources gravely weakened by adverse reaction.

I offer the Indian experience as set forth by Dr Lall, and I quote: 'India has the most pervasive, restrictive and inward looking regulatory system of any developing country in the non-socialist world . . . The basic premise of (India's) set of policies . . . is a deep-rooted suspicion of market forces . . . In India it is taken as axiomatic that the government is omniscient and efficient . . .'.

I won't enumerate the various policies regarding foreign investment, prices, licensing, taxation, and marketing practices to which, as Dr Lall explained, this attitude has led. I will, however, quote you Dr Lall's assessment of their results: today 'there are shortages of many drugs, imports of drugs for which capacities exist in India are rising, and growth and investment prospects are . . . gloomy.

'The Indian regulation system,' Dr Lall concluded, 'is an object lesson in how not to manage the drug industry.'

India has not been alone. Sri Lanka is another country which supposed it could offer a better deal to its people by taking the profit out of the drug business. Sri Lanka opted for centralised government purchases of drugs from presumably cheaper sources, including the non-market economies of the Communist bloc. The result: a sharp drop in product quality, frequently interrupted supply, little if any of the anticipated cost savings. Once applauded, the Sri Lankan experiment is currently being aborted.

Yet even as this occurs, others grab blindly for the seductive 'quick-fix' of government regulation.

Bangladesh, for instance, proposes flatly to prohibit sales of all but those drug products it deems of greatest value. The impetus behind this proposal comes in part from the fact that a high percentage of the Bangladesh health-care dollar currently goes on medicines. But this is normal – and appropriate – for a country whose capacity to deliver other health-care services is severely limited. Critics have characterised industry's efforts to suggest more sensible solutions as officious meddling. Bangladesh need not listen to us. All Bangladesh need do is heed the lesson of its Asian neighbours.

Notwithstanding the wealth of evidence illustrating the folly of economic controls, one frequently hears it argued that such controls can be cost-free. Typically, those making this argument cite a country that has imposed a

new economic regulation and apparently experienced no ill effects – no price increases, no withdrawal of companies from their market.

They make either or both of two false assumptions. First is the assumption of the man who, having survived a little dose of poison, supposes it safe to take a large dose. Its corollary is that if restricting market access in, say, Bangladesh doesn't materially affect overall research investment by multi-national drug firms, research investment will not be affected if Kenya, Malaysia, Paraguay and New Zealand decide to follow suit. This is not true.

What Bangladesh does may not, by itself, be terribly significant, even though it has the effect of shifting costs to consumers in other countries. But if Bangladesh opts for a free ride on research, so will other countries. By the time the costs thus shifted achieve critical mass, it will be too late to avert the damage.

The second false assumption is that the effects of regulatory poisons are immediate – that, for example, if patent protection is reduced and negative consequences are not immediately visible, none will occur.

This is not true either. The link between regulatory change and corporate behaviour is not mechanical. Corporations are merely collections of human beings. They react like human beings. Corporate managers do not simply drop what they have been doing for years because one day a new regulation makes it economically unattractive. They may be reluctant to abandon the work of which they have made careers. They may have large investments that cannot quickly be liquidated. They may be in the midst of long-term projects that will be cheaper to complete than abandon, even if they must be completed on unfavourable terms. They may, like most of us, be optimistic enough to hope that an offensive new regulation will be perceived to be unwise and repealed.

There are, in short, many reasons why the effects of regulation may not immediately be evident. But those effects cannot be avoided for long. Those who choose not to acknowledge this, do so at their own peril.

Because our industry has sometimes been accused of crying poor, let me be careful not to overstate my concerns. I have not intended to suggest that even severe regulatory reaction will bring innovation to a standstill. The threat is not to progress. The threat is to optimal rates of progress. Prospective new medicines may not be irretrievably lost. What *will* be irretrievably lost is time. But time is important. Time, after all, is what people die in.

These dangers are sobering, assuming that foregone welfare sobers you.

Are they inevitable? I can't give you a certain answer. Whether we can prevent primary economic effects from producing secondary regulatory reactions – that in turn produce tertiary health-care losses – will depend to a great extent on how well we can make our public and our politicians understand what is at stake.

We need to explain the cost-benefit issue. We need to get people to look, not just at expenditures for new medicines, but at the savings those medicines make possible in other areas of the health-care sector – not to mention improvements in human well-being and productivity. We must also be ready and willing to respond to misguided proposals advanced at the local, national and international levels.

I have cited India, Sri Lanka and Bangladesh as examples of well-

intentioned but short-sighted over-regulation. One other recent proposal bears mentioning.

I refer to the astonishing proposals that emerged last year from the Nairobi convention on revisions to the 100-year-old Paris Convention on intellectual property rights. Advanced by the developing countries, with little opposition from Western nations other than the United States, these proposals would seriously weaken patent protection in the developing world by providing for exclusive compulsory licensing and outright revocation of pharmaceutical patents where local manufacture is not undertaken very early.

The ill effects of the Nairobi proposals would be felt most strongly by the very peoples whose interests they purport to further. Third World markets would be shunned. The flow of investment towards the Third World would be curtailed. And research on drugs for tropical diseases and other inflictions peculiar to Third World markets would diminish or cease.

Like so many regulatory proposals, or so-called 'reforms', advanced by people who do not understand or choose to ignore how the engine of economic activity functions in a market economy, the Nairobi proposals rest on the flawed assumption that, because our accounting system records costs and profits on separate lines, profits are something extra – unrelated to costs. And that so long as accounting costs are covered, profits can be captured by the state without harm to the economic activity that generated them.

But the profits are a cost, too. Indeed, profits are the most important cost of all, for profits are the cost of putting all the other costs to work. Reducing or eliminating profits won't yield goods and services for less. Reducing or eliminating profits will simply generate fewer goods and services. Any Third World economy that insists on treating profit as something extra to be appropriated will find itself grabbing at air. Any developed country that refuses to protest such folly puts short-term international political harmony ahead of reason, subverts its own interests and undermines the interests of the Third World countries which, by pursuing such madness, only ensure membership in the Third World as their permanent status.

In conclusion, it seems to me that the pharmaceutical industry faces two challenges. The first is the scientific and technological challenge of creating more effective medicines to produce longer, more productive lives for people in all countries. The second challenge is to protect that scientific progress from well-intentioned but lethal government paternalism in industrialised as well as developing countries.

The latter challenge may prove more difficult than the first – but both must be met if we are to realise the full benefits of the Second Pharmacological Revolution.

Japan: the economic challenge

Shinbei Konishi
Takeda Chemical Industries, Japan

I wish to present to you today a general picture of the Japanese pharmaceutical industry, with special attention to some of its particular characteristics. There have already been a number of important English-language articles concerning the Japanese pharmaceutical industry. They include: 'Japanese Pharmaceuticals', published by *Scrip World Pharmaceutical News*; 'Challenge to Japan', from *SRI International* and 'Japan Drug Industry Review', by Yakugyo Jiho. Still, I think you might be interested in hearing first hand from a man who has been active in the business for a long time.

Let me begin with a brief review of the history of the pharmaceutical industry in Japan. Until the Meiji restoration in 1868, Japanese medicines had been mostly of local and Chinese origin. During the Meija era, however, Western medical science and drugs were introduced and rapidly replaced the traditional drugs. The first edition of the *Japanese Pharmacopoeia* was issued in 1886. With the outbreak of World War I in 1914, importation of drugs became difficult, and the establishment of a Japanese pharmaceutical industry was essential to meet the domestic need.

Today, Japan has become the second largest producer and consumer of pharmaceuticals in the free world, after the United States. Table 1 shows the values of Japanese drug production and foreign trade. As you see, imports far outweight exports.

The latest published records of the ten major Japanese pharmaceutical companies show that their average net profit is about five per cent of net sales, a far smaller figure than that reported by major US companies. On the other hand, outstanding accounts receivable are equivalent to about four months' net sales – more than the figures for major US firms.

TABLE 1 **Drug production values by therapeutic category and foreign trade**

	Production value (million Yen)			
	1979	*(%)*	*1980*	*(%)*
Total	3,042,302	100.0	3,482,177	100.0
Antibiotics	658,009	21.6	814,320	23.4
Circulatory system drugs	309,332	10.2	377,757	10.8
Other metabolic drugs	315,601	10.4	363,950	10.5
Central nervous system drugs	304,503	10.0	344,197	9.9
Gastrointestinal drugs	240,960	7.9	256,830	7.4
Vitamins	210,813	6.9	216,249	6.2
Topical drugs	189,942	6.2	197,984	5.7
Others	813,142	26.7	910,890	26.2
Imports	218,779	—	262,363	—
Exports	83,463	—	93,901	—

The liberalisation of foreign exchange for the importation of drugs in 1971, followed a few years later, in 1975, by the free approval system on foreign investment in the Japanese pharmaceutical industry, stimulated the Japanese companies to strenghthen their production capabilities in order to cope with the foreign competition. These government measures, together with the introduction of the product patent system in 1975, have forced Japanese companies to invest heavily in research and the development of new drugs. This is clearly apparent from Table 2 which shows Japanese research and development expenditures.

In the pharmaceutical field, new product development goes hand in hand with an exceptionally heavy responsibility for product quality and safety. Good Laboratory Practices similar to those in the United States were introduced in March of this year under the administrative guidance of the Ministry of Health and Welfare. Earlier, in 1979, our Pharmaceutical Affairs Law underwent a major revision. The prime objective, set forth in the first article of the revised law, was to assure the quality, effectiveness and safety of drugs. At the same time, a fund for the relief of those suffering from adverse reactions to drugs was established.

This Relief Fund is a state-authorised corporation providing prompt assistance in cases where serious adverse effects result from drugs which have been correctly used as prescribed. It does not apply to the improper use of drugs. Manufacturers pay into the Fund 0.01 per cent of their annual sales, based on drug prices set by the health insurance system. In cases where it becomes evident that an individual company has been negligent and is liable for the damages, further payment from the Fund is suspended.

In recent years, many articles have been written regarding future prospects for the Japanese pharmaceutical industry in the international environment.

In his article 'Japan in the 1980s', which appeared in the June 1981 issue of *Pharmaceutical Executive*, Leif Schaumann wrote that Japan is not yet a noticeable competitive factor in the pharmaceutical business outside Japan, and that to gain just a one per cent share by 1990, the country must invest billions of dollars in domestic industrial reorganisation, foreign marketing and distribution networks and successful development of new chemical entities of interest to the international market.

In the 29 August 1981 issue of *The Economist* there appeared an article entitled, 'Kill or Cure for Japan's Drug firms'. The introduction states, 'Not all Japan's industries are as slick and all-conquering as cars and electronics, and its pharmaceutical industry is constipated and uncompetitive.' But it

TABLE 2 **Pharmaceutical research expenditures in Japan**

Fiscal year	*Amounts of Exports (million Yen)*	*Increase over the Previous year (%)*	*% of net sales*
1974	79,157	22.9	4.37
1975	95,191	20.3	4.91
1976	109,537	15.1	5.05
1977	120,537	10.0	4.84
1978	134,714	11.8	5.00
1979	176,905	31.3	5.53

also says that if the new strategy works, then the bigger companies will make an assault in the 1980s.

Under the headline 'Auf dem Weltmarkt will Japan bis 1990 ein wichtiger Konkurrent sein', an article in the 23 February 1981 issue of *Die Welt* said that, for the time being, the chances of the Japanese are not estimated to be high, especially in respect of time. They hold more modest targets compared with other branches of industry.

And finally, Yoshio Yano, Executive Director of International Pharma Consulting, says in the conclusion of his work 'The Viability of the Japanese Pharmaceutical Industry Internationally' that the Japanese pharmaceutical industry has made remarkable progress in the last fifteen years, and there is every chance that it will continue to do so. Although its pace looks slow and there are still problems to be solved, its future is worth watching.

These four articles reflect American, English, German and Japanese views concerning the outlook for the Japanese pharmaceutical industry in the international market. I think each of the four rightly depicts some aspects of the Japanese pharmaceutical industry.

Some industry observers in the West maintain that the Japanese pharmaceutical industry is now treading the same path that her automotive and electronic industries did some time ago, and will come to dominate the world drug market in the late 1980s. I cannot go along with that view.

My own view is that the major future stategy of Japanese companies will be to continue to increase their investments in research and development. However, a large percentage of their research achievements will be licensed to foreign companies for overseas markets in exchange for the licensing of foreign products in Japan to meet domestic needs. Only a few Japanese companies will put up their own flags in developed countries, either by joint ventures or wholly-owned subsidiaries.

The slogan adopted by the World Health Organisation on Health Day this year is, 'Add life to Years'. In Japan we have a saying, 'Sukoyakani Oiru' which means 'Grow old in good health, mentally and physically'. I foresee that the emphasis in Japanese research efforts will shift from antibiotics to new approaches to combating the diseases associated with ageing. Demographic changes will, I think, dictate this. Japan is a small island nation of only 378 thousand square kilometres, but is densely populated by 117 million persons. In 1981, the average life span for Japanese men was 74, and for women, 79. The number one cause of death is cancer, followed by cerebral apoplexy and heart diseases. Although the annual population increase is less than one per cent, it is estimated that the number of persons over 65 will increase to sixteen per cent of the total population by the year 2000. Thus, our demographic structure is becoming similar to that of Europe, with a large proportion of elderly citizens. There is great concern, therefore, to find new ways to treat senility and the degenerative diseases of ageing.

It is my opinion that Japanese research activities will also continue to utilise genetic engineering and cell technology. Phase II clinical trials to investigate the efficacy of alpha interferon produced with recombinant DNA technology in the treatment of several types of cancer and viral infection will start this fall. The technologies of genetic engineering and cell fusion have become powerful tools for analysing the mechanisms of immunity

and causes of metabolic disorders and cancer. At Japan's Osaka University a multi-disciplinary research centre has been created to concentrate in these areas.

In summary, the Japanese pharmaceutical industry has grown to rank second in the free world within a comparatively short period of time. The liberalisation of imports and foreign investment have stimulated Japanese companies to invest more in research and development of new drugs in order to compete with foreign companies. Imports, however, still far outweigh exports in the international market. Japanese pharmaceutical companies will certainly become more active in international trade, but they are unlikely to attain the dominance of either the Japanese automotive or electronic industries. Research and new product development will be the predominant concerns of the industry in the foreseeable future, and the research emphasis will shift from antibiotics to drugs useful in treating the infirmities and diseases associated with ageing, reflecting a change in the Japanese population to more nearly that found in Western countries. Genetic engineering and cell fusion technologies will also be developed vigorously.

I look forward to the day when the Japanese pharmaceutical industry will have developed and produced drugs reflecting deep insight into the aetiology of diseases, based on the discoveries in the medical and biological sciences – drugs which will truly 'add life to years'.

Discussants

DR RICHARD ARNOLD
Association of the British Pharmaceutical Industry

In responding to the preceding three papers I want to draw attention to some of the opportunities and dangers which will influence the extent to which the pharmaceutical industry in the United Kingdom will be able to play a role in the Second Pharmacological Revolution.

I think it is true to say that there are few countries where the international nature of the pharmaceutical industry is more apparent than in the UK. At least sixty per cent of ABPI members are foreign owned, and ABPI members themselves supply ninety-five per cent or more of the medicines used by the National Health Service. Whilst this preponderance of foreign-owned companies is certainly not unique, we do stand out I think in the extent to which many of the foreign-owned companies have developed fully integrated operations in the United Kingdom with major research facilities, basic chemical as well as pharmaceutical manufacture, and a substantial export business from this country.

The escalating costs of research to which Otto Nowotny has drawn graphic attention in his excellent paper have already brought us virtually to the point whereby research-based companies can exist only by trading on an international basis and yet locating their major investment in production, and especially in research, in very few countries. My remarks hinge on the fact that the precise location of research and production facilities, which to a large extent is at the discretion of the decision makers in the companies themselves, is going to be greatly influenced by national government policies: favourable policies can attract investment and an unsympathetic government can drive it elsewhere.

The fact that the United Kingdom has attracted perhaps more than its proportionate share (in relation, that is, to market size) of investment in research and production capacity over the past decades has been due to a considerable extent I believe to the generally realistic policies of a succession of governments of different political complexions. In particular, the Pharmaceutical Price Regulation Scheme (PPRS) to which the industry has bowed its neck for more than twenty-five years, does at least have the very positive feature of seeking to encourage a strong profitable research and export-oriented pharmaceutical industry in the UK. The pragmatic implementation of the scheme by a small, very professional and tough group of civil servants has done much to encourage substantial investment in research by both British-owned and foreign-owned companies in this country, and at the same time it has succeeded in keeping drug prices at a very reasonable level (some perhaps would say too low a level).

The investment in research has certainly paid off if one looks at the discoveries that have emerged from the UK and foreign-owned laboratories here. At least ten of the twenty leading products on the market in the United Kingdom were discovered here and, although this pattern of usage obviously does not occur world-wide, British-discovered medicines have made very important inroads throughout the world. This innovative suc-

cess in turn has helped to put the UK high on the list of pharmaceutical exporting countries, and currently we rank in the top four, together with the United States, Switzerland and West Germany.

On past history the United Kingdom should be expected to play an important part in the Second Pharmacological Revolution, but whether we do or not depends very much on continuing government recognition of the dual benefits which the industry brings to this country. On the one hand it provides a constant supply of high quality and steadily more effective medicines which help to improve the health of the population. On the other hand it makes a very important contribution to the economic well-being of the country. In 1980 the pharmaceutical industry ranked fourth among sixty-three different United Kingdom exporting industries, and it generated nearly seven per cent of the total UK visible balance of payments from abroad.

At this time of considerable economic recession and with the determined efforts of the Government to confine public sector expenditure, there are signs that Government support for the industry may come in for critical scrutiny. After all, the UK pharmaceutical industry is dependent on the public purse for nearly sixty per cent of its income. Short and medium-term expedients to reduce the drug bill could be a major discouragement to those decision makers in the industry who have to determine whether and where to invest in research and production. Such decisions taken at a time of what we hope is relatively short-term economic stress can, so far as we are concerned, produce very serious adverse effects which will last for decades.

Time does not permit a detailed analysis of the many devices a government might adopt to reduce expenditure on drugs. In any case, Otto Nowotny has done just that in listing the negative factors for innovation in his presentation. Nevertheless, I would like to underline some of those areas which could be especially relevant to the British scene and to which in a number of cases reference has been made by one or other of our political parties in the recent past.

I would first mention substitution, that is the principle of giving the right to the retail pharmacist to dispense a generic product against a script which specifies a branded product. This alone would do enormous damage to the industry, both research based and paradoxically to the British generic industry. It would destroy investment confidence, and the loss of export earnings alone would represent far more money than would be saved by the policy of substitution.

Secondly, I would mention the possibility of undue pressure on doctors to restrict their prescribing, for example, by removing certain products from the drug tariff so that they could not be made available to patients under the NHS, or by in any way giving a mandatory character to, say, the British National Formulary. One has seen very regrettable actions on the part of both the Dutch and Irish Governments in recent months in terms of restricted access to insurance schemes.

Thirdly, I would mention the question of restricting the availability under the NHS of any new medicine by virtue of supposed lack of clear-cut advantage over existing products. If research is to be encouraged, access to NHS prescribing should surely be on grounds of safety, quality and efficacy alone, as at present.

Fourthly, and I need hardly to expand on this, nationalisation of all or part of the industry.

Any of these factors could have an immediate adverse effect on investment confidence within the industry, and the effects would not easily be reversed. Apart from these very obvious dangers, there exists the more insidious threat of a squeeze on prices and profits. The continuation of a form of price control, perhaps not too dissimilar from the present PPRS, seems inevitable in the foreseeable future unless a government should choose to reject its fundamental principles by implementing any of the policies which I have just mentioned. But taking the optimistic view that this catastrophe will not befall us, it is nevertheless essential that the industry should be allowed a reasonable level of prices and consequently a reasonable return on investment in order to maintain a high level of investment in research. In that I am not talking just about research within industry itself, but I am talking about research which industry may support outside in academia. In this way, if the industry is permitted this adequate return, it can play an important part in the Second Pharmacological Revolution and in the economic recovery of the country at the same time. I am a natural optimist, and I firmly believe that this is precisely what is going to happen.

PROFESSOR SIR BRUCE WILLIAMS
The Technical Change Centre

I do not think it is yet clear what the nature of the Second Pharmacological Revolution is going to be; it is not yet clear how far the new developments are going to make drugs more effective in dealing with the sorts of illnesses they now cope with, nor how far the development is going to create a breakthrough in the treatment of illnesses that do not at present yield very well to treatment by drugs. I guess that it will be some time before the effects of the revolution are at all clear.

What I think is clear and has been for some time is the need to keep the balance of expenditure on health care under review. That was stressed very much by the second presentation in this session, and I think very properly so.

I was responsible for the design of a very large teaching hospital in Australia some time ago, and in watching the developments in hospitals, even in the ten years between the time we started and the time we began to admit patients, I was conscious that many of the assumptions on which we had built that hospital had become quite outmoded. I was conscious that the balance between expenditure on drugs and on doctors and nurses had been changed, indeed perhaps should have been changed more than it was. I was conscious that people with illnesses for which they had been put in hospital and in some respects were still being put in hospital should not any longer be put in hospital, or at any rate not for more than day care, as a result of many changes in the efficacy of drugs and of the emergence of new drugs. It may be that this Second Pharmacological Revolution will accelerate that change and will make even bigger changes in our present approach to types of hospitals and the extent of hospitalisation. I think it is right to emphasise the need to keep that very much under review.

The second thing I think worth commenting on is that by the mid-1970s

that very remarkable post-war boom had come to an end. It was remarkable in the sense that growth rates were higher and the length of the boom was longer than any previous boom. But in a sense we are back in familiar territory because we are now in a serious depression, as we have been approximately every fifty years. It may be some time, judging from the experience of the past, before we climb out of this depression and achieve high growth rates again.

That has obvious implications for the likely development of drugs. There are I think two counter forces here. The first one is that because of the much lower economic growth rates, public finance is not buoyant and the claims on public finance (through, for example, unemployment) have risen quite sharply. In all countries that has led quite inevitably to questions about expenditure on health, including expenditure on drugs. I think it is almost inevitable that when international companies play an important part in the provision of goods there will be strong political questioning as to whether the goods are being provided on the right basis. That has happened here as it has happened in other countries. But rather than put the emphasis on distrust of international companies, I would put the emphasis on the lack of buoyancy in public finance. It is very important to come to terms with that, particularly if we are going to have a few more years – and it may be quite a few – where growth rates are low and public finance far from buoyant. If that is going to be the experience, we will continue to have pressure to economise on health expenditure and on other expenditures in which public finance plays an important part.

I think this depression has also made very obvious to pharmaceutical companies the importance of trying to create rather better growth in their own markets through product innovation. Obviously a great deal has been done and will be done to compete on price, but that is the sort of thing you run through after a few years; the critical opportunities for further growth come from product innovation. I know the companies will say, very naturally, that innovation is so much more difficult when markets are not expanding. That is true, but the need for product innovation becomes more urgent in the interests of the companies.

If you look back to past depressions you will find that despite the low profit margins there were in fact very many important innovations occurring not just in pharmaceuticals but in other industries as well. Such innovations can play an important part in helping countries to climb out of depression. Yet this mechanism is strangely neglected, especially by economists. Inevitably the achievement of innovative advance under conditions of economic hardship poses substantial difficulties for manufacturers but then again life under a competitive system was never meant to be easy.

Let me say something further about the competitive mechanism which was mentioned in all three papers, and is very frequently mentioned when there is discussion of the pharmaceutical industry. One of the major problems about the competitive mechanism is that it is a very difficult one to comprehend. Indeed it was once described by a distinguished Polish economist as a kind of blind man's bluff in that it persuaded people to go after profits but by its very nature destroyed the profits once they were generated, so forcing people to start all over again.

When the industry emphasises the importance of competition and how

tough life is and how creative competition can be in its ultimate effects, it is very important to keep in mind that by and large the mechanism of competition appears rather mysterious to most people. Indeed, if I can comment on the side, it is apparently mysterious to some of the advocates because they slip in certain things which are essentially modifications of competition in their own interests.

The important things to emphasise are I think these. Competition is created by law and it is a form of social control. The conditions under which competition will flourish keep changing and they need to be kept under review. For instance, as soon as the community places greater emphasis on environmental quality, governments are forced to change the conditions of competition through introducing new laws or administrative procedures. That is a continuing process and it will not go away. It will be an essential part of the political mechanism that all manufacturers have to come to terms with.

One of the ways of qualifying the competitive mechanism is the introduction of other legal devices such as patents. The introduction of patent protection predated the competitive system, but patents have played an important part in innovation within the competitive system. But this, too, is a difficult mechanism to comprehend and it is by no means clear that the existing patent systems are ideal. We have had reference to the diminishing value of patent protection because of the increased time taken to get approval to bring drugs into commercial use. That in itself points to one of the problems of most patent systems in that they are related to time and not to outcomes. There is a great deal to be said for re-thinking the basis of the patent system to get it away from time and to get it towards the returns on expenditure. I know that is a complicated issue and many people think that such a scheme would degenerate into a form of cost plus. But it need not do so and I think the industry would be well advised to think about this quite openly, because, as I say, there is a need to make the competitive mechanism and the control system much more understandable.

PROFESSOR ERICH KAUFER
Innsbruck University

My comments will be addressed to four issues: firstly, the role of patents and the tendency of free riding on other countries' R and D results; secondly, the impact of the New Mercantilism on the poor countries as a potential drug market; thirdly, is there a law of diminishing returns to R and D; and, fourthly, the shifting innovation possibility frontier for drugs and its implications for the future of the Japanese drug industry.

To start with I will consider the issue of patent protection, Since one of our distinguished speakers comes from a Swiss company I should like to review the Swiss experience with patents. It is well known that it was the brilliant French inventors who laid the foundations of what is now the chemical industry. The French law of 1844 granted product patents. And this fact contributed to the early decline of the chemical (especially dyestuff) industry in France. At that time Germany and Switzerland had no patent laws. Their companies freely copied the French inventions, and fierce competition among the German and Swiss companies stimulated the

search for cost-reducing processes. Thus, after a while the French companies, feeling no comparable pressure to reduce costs, were unable to compete with the Swiss and the Germans in third markets. And they lost even their home market once their product patents expired. When the chemical industry was firmly established, Germany introduced a patent law and threatened Switzerland to follow soon.

Why should a less developed country of today not do what Germany and Switzerland did with such apparent success yesterday?

However, what is defensible for a less developed country is to be judged differently for an already industrialised country. Countries like Canada, France, Italy, Sweden, and my home country Austria undermine the patent system by certain licensing provisions, price controls and the like for reasons quite other than industrialisation.

Here we have not rich countries exploiting poor countries. Here are some rich countries on one side trying to take a free ride on the R and D results of other rich countries on the other side. And the lessening of R and D effort induced by this kind of exploitation hurts all countries, the rich and the poor. Several decades ago, the grand old lady of our profession – Mrs Joan Robinson of Cambridge – gave us a name for this. It is a classic case of beggar they neighbour policy!

Secondly, the New Mercantilism. Mr Nowotny has rightly pointed to the vast, untapped market potential of the Third World where 80 per cent of the population has no access to the drugs they need. But why is that market potential so undeveloped? Well, these countries are simply too poor to buy and to distribute the drugs. So we have to ask, why are these countries so poor? A major reason for the sad situation lies in our general mercantilistic trade policy. We know that free access to our home markets by the export industries of the less developed countries is the main stimulus to their growth. However, whenever a less developed country gains a comparative advantage in some of our older industries like textiles, synthetic fibres, electric appliances or steel, we react by imposing tariffs, quotas or non-tariff barriers. Need I mention that the agricultural policy of the EEC ruins the agricultural sectors of many less developed countries, although these sectors are the cornerstone for entering a path of sustainable growth? We, and by we I do *not* mean the pharmaceutical industry but the member countries of the EEC, preach Adam Smith and practice Colbert. This ruins the future market prospects of the drug industry more than any other governmental measure.

Thirdly, is there a Law of Diminishing Returns to R and D? I do not dispute the existence of such a law in the narrow sense of a functional relationship between homogeneous quantities of inputs and output. However, this relationship is not what is of concern to us.

The direction and pace of technological change is determined by demand pull factors on the one side, and by the opportunities inherent in the technological base of an industry on the other side. I need not expand the point that various regulatory measures and the beggar thy neighbour policy of some of the rich countries reduces the demand pull for drug research.

We have a considerable amount of empirical research to the effect that the relationship between demand pull, as measured for example by new

capital investment, and the flow of inventions to these industries is *linear*. In this sense there is no law of diminishing returns to R and D.

The reason for the reduction in output per R and D pound is a different one. At the last OHE symposium (Medicines for the year 2000) Brian Cromie reported on a frightening trend. From 1970 to 1978 the percentage of Hoechst's world-wide R and D budget devoted to innovation declined from almost 50 per cent to less than 30 per cent, and Professor Mansfield recently reported that between 1967 and 1977 the proportion of basic research in all R and D done by American industry declined by one-fourth – mostly because of rising regulations. It is our rising aversion towards risks that is responsible for the decreasing output of innovations per R and D-pound: we wish to have relief, but we do not want to take risks!

A vicious circle is operating. According to the psychologist Festinger people are unable to live in a state of cognitive dissonance. Every politician and mass media communicator tells us that risks are intolerably high, and that we ought to be protected more. Though we are quite prepared to accept the risks, we cannot live in dissonance between our true preferences and the message we hear daily. We react by adjusting our preferences to what we are told. Thus our preferences toward risks become endogenous: the less riskier drugs become, the more safety we demand; the more we spend on R and D, the fewer innovations we get out of it!

Quite apart from the endogenous change of our preferences for or against risks, R and D expenditures tend to increase because drugs can be substituted for a healthy way of life. The more we are able to cure, the less healthy we tend to live. Thus we are likely to develop new illnesses as we cure old ones. Only some drastic reform of the health insurance system reverses that trend.

As far as I, as an economist, understand there is another serious problem. On one side the changing age structure of the population demands the development of completely new drugs, for example, against mental and chronic diseases. Yet the present practices of drug regulation make it very costly and risky to develop new biomedical models for searching for drugs. We continue to rely on the old models and get more of the same where we need more of the different. Furthermore, the development of drugs for long-term therapy is especially risky, time consuming and expensive as far as regulation is concerned.

I think we should not use the term 'Law of Diminishing Returns' as a label for behavioural and regulatory phenomena that it is our utmost duty to change during the next decade.

Finally, I want to consider the Shifting Innovation Possibility Frontier. The first pharmacological revolution was based on an innovation possibility frontier characterised by randomly screening a vast number of substances. Recent advances in biomedical knowledge make possible a more imaginative and rational approach. More and more the development of drugs is done by setting forth in advance very specifically the properties desired in a new drug. The molecules are constructed atom by atom to affect a pretargeted physiological process in the body or in a cell. This is a very fundamental change in the way R and D is conducted and diseases are treated. Not the symptoms but the causes of diseases will be treated for the first time in medical history. Some of the established companies will not

have the huge sums for the new type of R and D, nor will they be imaginative enough to respond to the fundamental change of the innovation possibility frontier. They will shift their R and D away from the search for new products to the search for less costly means of producing the older drugs. The emphasis on generic prescription or on variants of maximum allowable costs makes this shift attractive. Some other established companies will continue to search for new drugs. But they must be careful. Product patents are not a sufficient protection of one's market position, as the early history of the French dyestuff industry demonstrates. Only very imaginative searchers for new drugs will be able to withstand the competitive pressure on profit margins that is going to be exerted by the new type of large, very efficient mass-producers of older drugs.

These changes will give the Japanese drug industry its chance, because many new avenues are opened and old established advantages are destroyed. I do think that the Japanese drug industry has already proved how imaginative it is and will be. President Konishi has quoted from foreign sources that the Japanese drug industry is not yet a formidable competitive factor in world markets and would not be one in the forseeable future. I think these sources are wrong because they extrapolate a trend that has already been broken. My view of the future is one of a classic case of the Schumpeterian gale of creative destruction with the emphasis on the role of Japanese companies and on creativity.

GENERAL DISCUSSION

The methods and implications of restraining the growth of national drug bills and a variety of issues related to the economics of pharmaceutical innovation emerged as the two principal areas of debate following the third session of the symposium.

Opening the discussion on the first of these points, Dr A. Herxheimer (Charing Cross Hospital Medical School) sought to justify the action of Third World governments in their attempts to contain their pharmaceutical budgets. Referring specifically to the case of Bangladesh he argued that with severely limited foreign exchange resources available for expenditure on imported pharmaceuticals it is essential that such countries obtain the best value for money on the purchases they do make. He considered it completely inappropriate for these nations to be buying medicines which are of dubious value to the needs of the indigenous population and especially at prices which are excessive given *interalia* that the original research costs of the products have, in many instances, long since been written off. Consequently, Dr Herxheimer considered it quite justifiable for Third World authorities to act to restrict or prohibit the entry of products to their countries as they see fit.

In response Mr F. Fowlkes, emphasised the dangers implicit – ultimately to the funding of pharmaceutical research – in what is effectively the closing down of market access should such action be pursued in other nations of the developing world. Nevertheless, he expressed sympathy for the Bangladesh government whose overriding priority must inevitably be the welfare of its own people within its budgetary constraints.

That the Bangladesh Government should not be criticised for taking decisions it considers to be in the best interests of its population was a view shared by Mr S. M. Peretz who had recently returned from a visit to that country. He did point out, however, that 90 per cent of drug sales in Bangladesh take place in the private sector so that the action of the country's Government is one that will primarily affect that particular sector. Yet, as Mr Peretz emphasised, the needs of the developing world are not going to be met simply be restricting drugs to the private sector. Instead, the requirement is to ensure the availability of medicines to all inhabitants of the Third World. In this context it would be in the 'enlightened' self-interest of the pharmaceutical industry to try and find ways of supplying drugs to those people at the minimum possible cost. It should at the same time be recognised that such a strategy is not going to be, in commercial terms, 'a crock of gold' for the industry. At best it might provide some incremental business to fill some of the factories that are not currently operating at full capacity.

Mr R. D. Douglas (Pfizer Europe) reminded the audience that drug cost containment measures are also becoming increasingly prevalent among the industrialised countries. Of potentially considerable harm, in his view, is the use of restricted drug formularies or negative lists. He noted that since the middle of 1981 such restrictions had been threatened or actually introduced in Austria, Germany, Ireland, the Netherlands, Greece and Portugal. This trend is disturbing and led Dr R. B. Arnold to comment that the industry would appear not to be doing enough to communicate to national authorities the view that such policy decisions are not in the long term public interest.

The second main theme of the discussion period was introduced by Mr C. Englehorn (Boehringer Mannheim GmbH) who argued that in times of severely restrained buoyancy in public finance, drugs offered one of the most efficient ways of keeping down or lowering the cost of health care. This contention was in fact challenged by Lord Vaizey who suggested that drugs might instead be cost raising because the impact of their introduction has been to facilitate therapeutic intervention in diseases which had hitherto been left untreated. Implicit in this observation is the potential danger that, in an era of negligible economic growth such as that now facing Britain and many other industrialised countries, whatever funds are set aside for health care might tend increasingly to be channelled away from areas which appear, superficially at least, to be cost raising and directed elsewhere – perhaps to those which are more politically vocal. In other words, finance for the Second Pharmacological Revolution may be significantly less forthcoming than it was for the first wave of pharmacological advance which took place in that remarkable period of post-war economic boom. The pharmaceutical industry is thus now faced with the pressing problem, in this changed set of economic circumstances, of arguing its case that the potential benefits of the Second Pharmacological Revolution are such to justify continued official support for its research programmes.

The complex issue raised by Lord Vaizey of the economic consequences of pharmaceutical innovation drew the response from Dr B. A. Gennery (Lilly Industries Ltd) that pharmaceutical advance has in fact been cost saving in many instances. Thus without psychotropic drugs, for example, there

would need to be twice as many hospital beds for long-term psychiatric patients as are currently in use. He also made the point that the escalation of health care costs is more a function of the widespread use of high technology in medicine than the consumption of pharmaceuticals. Furthermore, he argued that the former techniques are often employed on a considerably less well-founded scientific basis than is the case with drugs and expressed the belief that one of the challenges of the 1980s is to ensure a more consistent evaluation of all therapeutic and diagnostic procedures entering medical practice.

Returning to the problem of pharmaceutical industry spending on the discovery of new drugs, Dr A. Herxheimer suggested that the costs of research and development might be kept down if less effort was directed to the evolution of 'unimportant' medicines. Mr O. H. Nowotny replied that there are great dangers inherent in the use of such terminology because apparently 'insignificant' advances often yield disproportionately large benefits for specific groups of patients. It would of course be extremely useful if such benefits could be measured or demonstrated but as Mr J-P. Poullier (Organisation for Economic Cooperation and Development) commented there is unfortunately a dearth of appropriate epidemiological data. Finally, it should also be emphasised that pharmaceutical innovation does in fact more frequently take the form of a series of 'incremental advances' rather than a single innovative leap of substantial proportions. Consequently it can be highly misleading to judge a specific phase of progress out of its proper context.

SESSION IV

THE ROLE OF THE REGULATORS

Chairman Professor Rosalinde Hurley
Queen Charlotte's Hospital for Women

Professor Hurley, who holds the chair of microbiology at Queen Charlotte's Maternity Hospital and is currently chairman of the Medicines Commission, kindly agreed at very short notice to act as chairman for the fourth session of the Symposium in place of John Maddox, the editor of *Nature*, who was unexpectedly prevented from being present.

Europe: the role of the regulators

Professor Sir John Butterfield
University of Cambridge

My intention this morning is to present some idea of the job of the regulatory authorities, the interactions in which the latter are involved and the qualities demanded of the individuals engaged in such work. When I refer to interactions I mean the problem for the European regulator as between himself as a national regulator and his European interests. I shall also talk briefly about the interaction between the European regulator, the American regulator and those who concern themselves with pharmaceutical products in the developing world.

To begin with then, why do I describe the European regulator as a 'jack of all trades' (Table 1)? It is because so often one hears that the people who have really heavy responsibilities in this world are described in many places as just being jack of all trades and master of one!

When I speak to my freshmen in Cambridge I explain that to be a good doctor in the days of ancient Greece four qualities were required – courage, knowledge, a sense of style and temperament, and judgement. I believe that the quality regulators must possess – whether in the World

TABLE 1 **The European Regulator in Summary**

Jack of all trades and master of one	Foresight
The job	
The framework	
Interactions to be faced	
The qualities called for	

Health Organisation, the FDA in the United States or regulatory bodies elsewhere – is related to three of these: it is foresight. They must be masters of this quality.

As I have set out in Table 2 regulators have to take on board a facilitating responsibility and this can impose a heavy burden on the civil servants concerned. Facilitating requires a certain kind of person: one who is able to see ways of helping things forward. I am using the EEC as my model here because that is where European regulations are mainly lodged. So European regulators have to take responsibility for facilitating the availability in Europe of human and veterinary medicines.

I have included in the second part of the definition (Table 2) the terms, safety, efficacy and quality. These words are the three main keystones of the UK Medicines Act and they are clearly the main themes with which we are involved. It will also be noticed that I have referred to the 'required quality'. We are hoping in Europe that we shall have a standard quality across the market. Before the Treaty of Rome there were instances where the quality of products exported from some countries was not all that should be required.

I shall not tell you any of the stories that we have heard in the past about drugs of an inadequate standard which came from this or that country. Suffice it to say that anyone who is a regulator is also something of an educator – trying to raise standards throughout the group of nations for which he is responsible. It is a tough job, so that only the paragons of virtue that we find in central authorities are competent to do it!

What about the framework (Table 3)? It is very important to recognise that the proliferation of regulations concerning the pharmaceutical industry originates from the terrible Thalidomide tragedy of 21 years ago.

One of the important points made in the Marre report, which looked back on the Thalidomide tragedy in Britain, considering the question of compensation, was that the compound was seen to be and was put forward as a possible advance on the barbiturates, because there was an incredibly high ratio between an effective dose and the lethal dose. It was because of

TABLE 2 **The job of the regulator**

European regulators have to take responsibility for facilitating the availability in Europe (EEC) of human and veterinary medicines which are safe, efficacious and of the required quality.
key words – responsibility
safe – efficacious – required quality

TABLE 3 **The framework**

Background –	Origins of present drug regulations
	The Treaty of Rome
	Initial directive
	British entry
Present framework –	Subsequent directives
	Present EEC committees

that huge ratio that it seemed such a sensible drug to give to pregnant ladies. As we know, it opened everyone's eyes. But we are not here to re-examine that episode. I do think, however, as we move towards the end of the century, that we may find that it was a dreadful blessing in disguise. After a very difficult period, I believe that the pharmaceutical industry throughout the world is emerging from under that dreadful cloud. For a period the industry was a very handy whipping boy for anyone who wanted to whip something, whether it was in a debate, in a newspaper or elsewhere. I believe that the process we are talking about today is all part of the aftermath of that tragedy. It has also been a sort of purification.

The problem about the Common Market is that the members joined at different times. The United Kingdom failed to get in at the time when the Treaty of Rome was drawn up, membership not being gained until the 1970s. By that time regulatory procedures had been well established. That was a disadvantage because it is very hard to make changes once things have started.

One of the prime objectives of the Community is to help goods move freely throughout Europe. In the pharmaceutical world, however, there have been forces which have tended to pull in the opposite direction. The Thalidomide tragedy, for example, generated considerable pressures in each country to establish effective regulatory systems. But the absence of a concerted 'European approach' has given rise to sets of dissimilar national regulations of varying adequacy. In the University of Cambridge Clinical School there are 12 departments between which there exist quite marked differences in the principles governing examinations. Is it really fair to expect a greater degree of unity between nations?

I do not think that the various Directives relating to medicines are very well understood among the medical profession, although this may not be true for those of you who have to work with, and wrestle under them. The starting date was in 1965, with the 65th Directive (Table 4). This provided for a common basis in dealing with applications for licences for proprietary medicines and their labelling. It was hoped that they would be distributed and flow freely throughout the Common Market.

Britain joined the EEC in 1973 and thus played a part in the drafting of the subsequent Directives shown in Table 4. Directive 318 is widely referred to as dealing with standards and protocols. It is both a bulky document and a highly technical one. It is concerned with the specifications, testing procedures and the types of analysis that are required in striving for high quality, efficacious and safe drugs.

The next Directive, number 319, is concerned with the duties of those experts involved in the preparation of applications in each country and the responsibilities of the member states in verification. The Directive set up a Committee for Proprietary Medicinal Products – the CPMP. Finally, the last Directive shown in Table 4 relates to the important issue of the colouring matter that may be employed in medicinal products.

I now want to turn my attention to the different committee structures (Table 5). The CPMP makes one of its members chairman and that is done in rotation. On the Medicines Commission we used to hear a good deal about what was going on in the CPMP and the Pharmaceutical Committee from our representatives there and from the leaders of our teams. It is clear that

TABLE 4 **The Directives**

65/65/EEC
A common basis for dealing with applications for licenses for proprietary medicines and their labelling.
(1973 UK entry into EEC)

75/318/EEC 'Standards and protocols'
Technical information regarding specifications analysis and testing needed with applications.

75/319/EEC
The duties of those experts involved in the preparation of applications and the responsibilities of the member states in verification.
Established the Committee for Proprietary Medicinal Products.

78/25/EEC
List colouring matters that may be used in medicinal products.

TABLE 5 **Committee structure**

Committee	*Chairman from*	UK *Rep*
Committee for Proprietary Medicinal Products	Members	DHSS
Pharmaceutical Committee	Commission	DHSS
Standing Veterinary Committee	Commission	MAFF

one of the problems about the Common Market is that when our own man is chairman we may have some advantages over those nations which are waiting to get their chairman in. Our representatives on EEC committees are DHSS staff. On the Pharmaceutical Committee the European Commission selects the chairman and the DHSS again puts up the representatives from this country. In the case of the Standing Veterinary Committee the responsible ministry is the Ministry of Agriculture, Fisheries and Food.

Focusing specifically on the CPMP (Table 6), membership is drawn from officials who have responsibility for the relevant work in their own countries. Obviously such individuals possess a very detailed knowledge of their own set-up, and are therefore among the best people to recognise where there are international differences. It is much better to have professionals who are dealing with these affairs in their own country, than to send in a lot of professors to do it!

The CPMP can take expert advice and frequently does so. Indeed, some expert bodies feel that it is within their purview to lobby so that they can

TABLE 6 **Committee for Proprietary Medicinal Products**

Members are officials responsible in their own countries.
Can take expert advice.
Harmonise information and criteria used by individual member states.
Progressive use of provisions of 75/319/EEC by 1990.
Holders of licences to manufacture or import must have permanently and continuously the services of 'qualified persons.'

put their point of view to the CPMP. I am never quite sure whether that is acceptable but I have heard people imply that they intend to do it.

The CPMP has to harmonise information and criteria used by individual member states, so that by 1990 there will be a general harmony of the drugs used – not only the drugs that are coming on to the market but all the drugs that are currently being sold. The review of medicines, both in Britain and in Europe, is an enormous task, given the large number of drugs from the past that have to be considered.

The people who are involved in holding licences must have their own expert; in other words, one cannot go into the manufacture of antibiotics unless one has a microbiologist on the staff who knows about the subject. That is just the sort of improvement in the professionalism of this already highly professional industry that is essential.

The CPMP is very much concerned with the tactics of the great drive to promote the free flow of drugs, whereas the Pharmaceutical Committee (Table 7) is more concerned with strategy. The latter's terms of reference are to examine any question related to the application of the Directives raised by the chairman or members; to examine any question related to the CPMP; and it has to be consulted by the Commission before any new Directives about pharmaceuticals are drawn up.

I am not sure how often the UK Medicines Commission has been consulted about governments' future plans. It certainly has in my time, for example about the surveillance of tobacco products. But the beginning of the Medicines Act shows that the Medicines Commission is in a position to address advice to Government, and Ministers can use the Medicines Commission whenever they wish by appealing to them under the Act.

I said that I would try to demonstrate the problems of interaction, and I am very grateful to the Medicines Division for providing me with the results of a questionnaire completed at a seminar of national experts held in 1981. At this meeting the participants asked each other all kinds of detailed questions about how drug legislation worked in their respective countries. I have selected some of the questions to demonstrate that even now, several years after the Directives have been in force, there are major differences in approach to the appeal procedure (Table 8). This is a very important point. If there are differences in the appeal procedure, that underlines the complexities and problems in harmonising marketing procedures.

I have not had to go very far into the results of the questionnaire to be able to show that there are national differences which still need to be ironed out. That is the point I want to make. All drug regulatory bodies in all nations have access to experts, and that is good, but there are discrepancies as to whether they are obliged to seek the advice of experts.

The Table shows that this is not the case in Luxembourg, Italy and the United Kingdom. The defence – and it is a reasonable one – is that there are many instances in which common sense tells one that there is not a problem. The safety of medicines type of committee is composed of intelligent people and they will know when they need to call in the experts, so in those countries it is not obligatory.

All those who come forward to serve on national advisory bodies should understand that the advice given is not binding on the licensing authority.

TABLE 7 **Pharmaceutical Committee**

Members are senior experts from member states.
Terms of reference – examine any question related to
- application of directives raised by chairman or members
- CPMP – must be consulted by Commission regarding directives, especially 65/65/EEC.

TABLE 8 **Problems of approximation**

Some comparisons between the European *National* Regulatory Bodies 1981
(acknowledgements to Medicines Division)

	D	F	W/G	L	N	I	B	UK
Access to advice of experts by Licensing Authority?	√	√	√	√	√	√	√	√
Is it obliged to seek such advice?	√	√	√	No	√	No	√	No
Is it only when Licensing Authority refuses?	√	√	√	No	√	No	√	√
Is the advice binding	No	No	No	No	No	No	No	No
If refused can applicant appeal to higher body?	√			√	√			√

But the responsibility does rest with the European regulators. They cannot duck the fact that they have got to take the decision, but there is no part of the law which says they have to take as binding the advice given by experts.

Can the applicant, the pharmaceutical firm, appeal to a higher body if its application is turned down? As Table 8 indicates, in some countries it can and in others it cannot. These findings show therefore that there are still many disparities, some of a philosophical nature, to be smoothed out.

Looking to future developments, Table 9 specifies three distinct areas: new arrangements for the joint consideration of applications to place products on the market; amendments to administrative, medical and scientific details; and the provision of guidelines for testing for safety and efficacy. The latter stems from growing concern in some quarters at the extensive testing procedures required of the pharmaceutical industry in the pursuit of safety. Increasingly, many medical minds have come to support a greater emphasis on post-marketing surveillance because of the difficulties inherent in animal models as reliable predictors of medicines used in humans.

TABLE 9 **Future developments**

- new arrangements for joint consideration of application to place products on market
- amendments to administrative, medical and scientific details
- guidelines for testing for safety and efficacy.

I now want to return to the paragons of virtue that the various nations select as the European regulators (Table 10). They must indeed be paragons, look what we have to ask of them. They must have robust health. It is clearly helpful to be a linguist. Anyone who has been part of an international conference knows how helpful it is to be able to talk somebody else's language and to understand the discussions that take place!

It is also very important to have the right personality. These poor regulators have to manage and to damp down the ardours and enthusiams of their own pharmaceutical industry, and push with the corporate wish for care and regulation, and yet at the same time, when self-interest is occupying the mind of the chairman of the committee, the regulators have somehow to be able to disarm the other folk and get them to relinquish a little of their national sovereignty.

I am reminded of a famous 1908 publication in Cambridge called *Microcosmographica Academia*. It is full of advice to a young university politician. Right at the beginning it says: 'In the fullness of time, when you have reached full maturity – somewhere about 50 – you will be very intrigued to discover that you have developed all kinds of idiosyncracies that people are having to learn about to square you, to get things done and to get your support. The people who come pressing you on this will be the young men in a hurry. You may wonder what they are in a hurry to do. They will be in a hurry to get rid of you!'

I am certain that a regulator must have a good legal turn of mind. It is invaluable also to have some scientific knowledge. It is important to have some grasp of the issues surrounding the pharmaceutical industry and to display a degree of sympathy. A regulator must have a general grasp of European history – about Bismarck engineering an invasion of France, knowing as he did that the French Napoleonic regiments were scattered in every town in France and that it would take them a long time to mobilise, whereas his regiments were all ready to go, town by town. It is essential to have a grasp of world economics and markets, and to be sensitive to the rest of the developed world. If bioengineering produces all the necessary

TABLE 10 **The European Regulator needs to be a paragon**

Robust health	–	Brussels flights – hotels – diet – lack of exercise – 'pressures and phone calls'
Linguist	–	helpful
Right Personality	–	for own and other nationals? – 'diplomatic'
Good legal mind	–	essential
Scientific knowledge	–	invaluable
Grasp of pharmaceutical industry and its problems	–	foresighted
General grasp of:	–	European history
	–	European and world economics, markets and demography

Needs to be a quick learner, flexibly minded, finder of acceptable compromises.
Has a communicative and educative role, including generating motivation about his responsibilities.

insulin by genetic manipulative procedures, what will happen to the insulin production for the 70 million diabetics in the developing countries?

The regulator must not only have a grasp of his own country but a feel for the rest of the world. He must understand demography – that there are 1,000 million people in China, 300 million people in Europe and a big market of about 300 million in North America.

We can see, then, that European regulators will need to possess many virtues. One of the things that I admire about them, through my contact with them via the Medicines Commission, and from one of them coming to talk to us, is their willingness to listen and absorb ideas. That, I think, is the hope for the future. They will inevitably come to appreciate their responsibilities and to be concerned with safe, efficacious, high quality medicines.

The United States: the role of the regulators

Dr Arthur Hayes Jr
Food and Drug Administration, USA

This symposium has set an ambitious agenda for itself, and I hope that the questions it raises will provide the focus for dialogue about the regulatory process in the years to come. As I looked over the programme, in fact, I made a reassuring discovery. There seems to be a growing acknowledgement that the process by which new drugs are reviewed for safety and efficacy is now viewed as something of a barrier in many nations.

The change is striking, for not too long ago the 'drug lag', as critics of the US Food and Drug Administration were fond of pointing out, seemed to be an American phenomenon.

I first became aware of this shift in attitude about a year ago while attending a conference in Ottawa, Canada. After one of the sessions, a Canadian journalist saw my name tag and breathlessly asked, 'Dr Hayes, some observers here think that Canada has developed a drug lag'. And then, as if that phrase were new to me, she asked, 'Do you have a similar problem in the US?'

'Why, I'm amazed that you don't already know,' I replied in mock surprise, 'that the US is the southern distributor of drug lag'.

The lesson of this anecdote – one that is reflected in the topic of this symposium – is that the new drug review process is an international issue. No one nation is particularly guilty of unduly delaying the marketing of innovative new therapies; no country has yet evolved the perfect regulatory framework for drugs.

These are important observations. There was a time when the FDA, for one, would find itself in an awkward position whenever drug lag was mentioned. We would say, in essence, 'There's no drug lag, and here's what we're doing about it'.

As I see it, the phrase 'drug lag' inappropriately mingled two concepts. There was, first, a regulatory dimension, one that involved delays in the marketing of products. Proponents of drug lag would often link this delay with what they argued was a decline in pharmaceutical research.

The theme of our symposium, I would assert, eloquently refutes this second claim about drug lag. But it also asks, appropriately, how will the regulatory process affect the products of the current pharmaceutical revolution.

That's the question I want to explore with you today, starting with the current situation in the US and then considering, from my perspective as US Commissioner of Food and Drugs, the nature of drug regulation as an international phenomenon.

I am pleased to report today on a number of exciting and encouraging developments underway to improve the drug review process in the United States. This effort has become one of my primary objectives as Commissioner.

Fortunately, part of this initiative was already underway when I arrived at the FDA. The Bureau of Drugs had begun an internal review of its policies and regulations in 1979 – with the goal of streamlining the entire drug approval process.

This massive project has become known in the corridors of FDA as the 'IND-NDA rewrite.' Please don't be put off by its bureaucratic name. 'IND' stands for the exemption we give an 'investigational new drug', the FDA's approval to begin clinical research on a new chemical entity with therapeutic potential; 'NDA' is short for 'New Drug Application', the document upon which the FDA bases its decision about the safety and efficacy of the new compound.

Despite its ugly-duckling name, this initiative will soon begin to produce results. Indeed, just about a year ago I appointed a task force within the FDA to study the drug approval process, including not only human prescription and over-the-counter drugs but veterinary drugs, medicated feeds and by extension, medical devices and even certain food additives and colours. The principles are often the same. We are about to forward a draft of our IND improvements to our parent Department of Health and Human Services.

The NDA portion of this effort is much further along. We will formally propose changes quite soon, and our goal is to have them take effect sometime next spring. Let me discuss what I consider to be the most significant of the changes we hope to introduce.

The NDA rewrite suggests two sorts of changes. The first involves improvements in efficiency that can be made without compromising the quality of the final decision about a drug. The second focuses on strengthening some aspects of drug regulation, while eliminating other requirements that do not contribute substantially to assuring the safety and efficacy of products.

Here, we seek a balance between our commitment to bring new therapies to market just as quickly as possible and our resolve to maintain the high scientific standards of safety and efficacy required by law.

One very important change that should result in greater efficiency is the provision for a new appeals process for resolving, in a fair and prompt manner, disputes between FDA reviewers and drug companies. In this proposal, FDA recognizes that many decisions involving new drug review rely on judgement and that legitimate areas of disagreement are bound to emerge.

This appeals process provides for prompt resolution, at a higher level within the FDA, of disputes involving new drug applications so that the NDA review does not get bogged down. Through this new process we hope to establish a forum where scientists from industry and government can meet, exchange views, and reach a conclusion. We are confident that the appeals process will help us carry out our mandate more efficiently.

Other significant proposals include the following:

- *Restructuring the NDA* to permit parallel review by FDA's different review groups.
- *Relying on detailed tabulations of case report forms, rather than the case reports themselves.* This change should increase efficiency by reducing the sheer physical bulk of new drug applications. Firms will be required to keep

all case report forms, and to submit them to the FDA in instances where patients die or drop out of studies and otherwise upon request.

– *Broadening reliance on foreign data.* FDA will consider data from foreign studies according to the quality of the data and their applicability to the US population. In the appropriate cases, it should allow safe approval of products without requiring costly, additional domestic studies.

– *Setting appropriate deadlines for FDA review.*

During our review of the new drug regulations, we also found two important areas where adequate public health protection was lacking. And so we are moving to correct these as well, particularly as they relate to the safety of patients:

– FDA will propose to require companies to update recent information about a drug's safety while that drug's application is still under review. This change will assure that approval decisions are based on the most current safety data available.

– Following through on the same safety theme, we will be strengthening our post-marketing surveillance system. The proposal contains a 15-day 'alert report' of any fatal or life-threatening drug experience and 30-day reporting for the rest. Recent experience has reminded us how important post-marketing surveillance can be in protecting the public safety, and we believe this system will achieve the necessary public health protection.

I have no doubt that these proposals will increase the efficiency of our system and that they will improve the public health protection we provide. We hope to have these improvements in place by the Spring of 1983.

I've outlined these changes today to provide you with examples of how we are approaching the particular problems we face in the United States. Other countries may have similar concerns. But each nation has built-in reasons why its regulatory approaches differ. And for the next few moments I'd like to concentrate, as an example, on what I consider to be some of the most significant differences between the US and the United Kingdom in the regulation of pharmaceutical products.

The first significant difference involves the law itself. Naturally, our public health acts grew out of dissimilar circumstances and evolved along different paths. The current FDA proposals to strenghthen post-marketing surveillance and to require more prompt submission of safety data might prove superfluous in the UK, with its more centralised health care delivery system. Under the current regulatory scheme in the US, we have in the past made selected drug approvals contingent on post-market surveillance plans.

There are, moreover, significant variations between the contexts of enforcement for our two countries' public health statutes. The US Congress has issued explicit instructions that in a number of areas affect the way the FDA goes about its business.

The Administrative Procedure Act, for example, provides very detailed directions for the rulemaking process. Conflict-of-interest provisions also strictly limit outside financial interests and activities of Federal employees – and among these employees are experts the FDA hires as consultants to its advisory panels.

Perhaps the most striking difference between the US and the UK involves the Freedom of Information Act. This act, one product of what has become

known as the 'Sunshine in Government' movement, guarantees the public's access to most of its government's documents. I might add in passing that the FDA fills more Freedom of Information requests each year – a total of nearly thirty-four thousand in fiscal year 1981 – than any other agency of the US Government.

The varied contexts for regulatory actions underlie what is probably the most essential difference between our two countries' regulatory systems. This difference involves accountability, a concept that is fundamental to a civilised regulatory system embodied in law.

The Food and Drug Administration works under a system of accountability that, to officials in the UK and elsewhere, may seem curious. The FDA is part of the Executive Branch. Its Commissioner is appointed by the Secretary of Health and Human Services and answers directly to him. The Secretary, in turn, is appointed by the President.

In addition – and this is where the accountability becomes interesting – the Commissioner also answers in a very fundamental way to the United States Congress. For it is the Congress that enacts that statutes we enforce; and Congress, subject to Presidential approval, makes the final decisions about our budget.

It takes no great leap of the imagination to envision circumstances in which this dual accountability could seem to pull us in two directions simultaneously. And the situation can change regularly, with Congressional elections being held every two years.

All of this is quite different here. After evaluating a drug, the Committee on Safety of Medicines makes its recommendation to the Medicines Division. The Division in turn passes its recommendation to the Licensing Authority. There is no separation of power between two branches of Government, and, as I understand it, no formal oversight review by the legislature in this country, and most especially not by the party that is not in power.

This arrangement makes for a different sort of accountability to the legislature than in America. Undeniably, it nurtures a different regulatory environment. I am also certain that comparisons between other nations would provide other differences in approaches to, and implementation of, drug regulation.

I have an ulterior motive for making this point about national differences. For now I want to examine for a few moments the similarities among our countries. If there is one point that has impressed me during my 18 months as Commissioner and during our review of the new drug approval process, it is this: that developed countries with advanced pharmaceutical industries live in a shrinking universe.

Let me explain. In the first place, drug development has become a truly international endeavour. Research projects commonly have an international scope, and multinational firms abound.

This growing interdependence among nations is one reason why our proposals call for greater reliance, as we reach decisions about new drugs, on data developed outside the United States.

If we are to cooperate as we should in the future, we should rely on up-to-date scientific methodologies – methodologies that will pass muster in other countries.

In short, we need closer cooperation among agencies that regulate pharmaceutical products. Regular international meetings, such as the Tripartite arrangement among Canada, the United Kingdom, and the United States, provide a useful forum.

But we need to do much more. Because we live in an ever-shrinking world – if for no other reason – it is essential that we share information. The inevitable differences aside, we must do everything we can to cooperate. Our recent experience bears out the need promptly to exchange information about adverse reactions to drugs or other health care products.

What do we need to accomplish in the coming weeks, months, and years to improve the efficiency of our pharmaceutical regulatory agencies?

The essential first step is prompt recognition that the driving force in the next few years is this Second Pharmacological Revolution – a Revolution that is producing an explosion of new therapies, new methods of study and investigation, new methods of analysis and new methods of production.

This vast outpouring of new products calls for a concomitant change in policies, procedures, and – perhaps above all – attitudes toward new drug approval.

Because time is running short, we must prepare quickly for massive qualitative differences in what regulation will require as advances in drug therapies continue. New compounds, innovative production techniques, and more complicated treatment regimens will all call for improved regulatory vigilance and creative problem solving.

Along with these qualitative changes in regulation, we should prepare for a greater quantity of regulatory decisions as the myriad new products make their way from the laboratory to the market-place.

Clinical testing will become at once more important and more difficult. To cope, regulatory agencies will want to work together to ensure that investigators are relying on today's best science – and that today's clinical methods will provide an adequate basis for tomorrow's regulatory decisions.

We will want to recruit the best people from academia and from industry to face this difficult regulatory challenge. And how can we ensure that regulatory agencies will be able to draw upon this talent?

The task will be especially difficult in times when every penny must be husbanded. When every minute an outside expert spends on governmental review work comes at the expense of his own research or professional duties, and when – in the US at least – potential conflict of interest difficulties loom. And they loom especially large as developing technology necessarily reduces the number of experts in any one specific area of expertise, and when these same experts are involved in the development and testing of the product.

All of these questions concern me. That's why in meeting with experts in industry and in universities across the United States, I've been urging them to share with the FDA some of their long-term plans. I'm asking them where they expect to be in five years, and what lines of research and analytical techniques they will be exploring.

For as Commissioner of Food and Drugs, I must ensure that my scientists and investigators keep abreast of scientific and technical advances. And I

need to have an idea, now, of what is coming down the road five years hence: otherwise, how can I guarantee that my reviewing officers, my laboratory scientists and my investigators will know everything they need to know to provide the assurance of safety and efficacy that the public expects and the law demands?

I must confess that, having set forth the regulatory challenges I foresee, I can produce no panacea or 'magic bullet' for responding to them. But I do have a couple of thoughts about how we should proceed.

It is clear that we can no longer afford national or parochial attitudes about the regulatory process. This observation applies, of course, to many subjects. In reading a book about the control of nuclear weapons, for example, I recently came across a phrase that I've been turning around in my mind.

'We live in an Einsteinian universe,' the author observed, 'and we are trying to make do with Newtonian politics.'

The gist of that thought applies to us here today. For like it or not, we are fast approaching the age of the magic bullet that once existed only in Paul Ehrlich's dreams. And yet if we fail to plan ahead, we will place ourselves in a position of evaluating Ehrlich's products with a regulatory apparatus that belongs to an older and more primitive era.

I want to leave you with two thoughts about how we ought to meet the coming regulatory challenge. The first is simply that we must cooperate – in sharing data on adverse reaction reports, in devising common regulatory techniques and methods, and in incorporating the best science possible into our clinical testing.

Second, we must not be so intent on finding a quick fix or on solving today's crisis that we fail to take the longer view that the Second Pharmacological Revolution demands we take.

Drug development and regulation have become universal concerns; there is a pharmaceutical interdependence of nations, and it involves difficult questions of science and economics. We must act as if there is a sort of international accountability.

And we must act as if the pharmaceutical world is growing smaller and increasingly interdependent – because that is precisely what *is* happening.

World Health Organisation: the role of the international co-ordinator

Dr Balu Sankaran
World Health Organisation, Geneva

In order to explain the World Health Organisation's position with regard to pharmaceuticals I shall draw upon two recent events. The first involves a most advanced and developed industrialised country, with all the modern technology at its command. The other concerns a poor, less developed, country (LDC) trying to set its house in order against all odds, with a heavy foreign debt, minimal productive capacity and very little knowledge in the field of quality control and manufacturing practices. I am therefore going to discuss first the 'benoxaprofen affair' and then the drug ordinance promulgated by a developing country.

The *British Medical Journal*, on 14 August, had an editorial on the lessons to be learnt from the benoxaprofen affair: 'It showed the dangers of current marketing policies by some pharmaceutical companies. It should make doctors think and question their willingness to prescribe new drugs. The public will want to know whether the Department of Health could improve its mechanisms for early warnings of side effects.'

The World Health Organisation, as soon as it was informed of the apparent potential risk associated with the use of this drug, sent information on it to all national regulatory agencies and drug authorities by telex indicating that the drug had been withdrawn by the United Kingdom because of suggestions that the drug had hepatotoxic and renal toxic properties – at least when used in the elderly. As far as we are aware, there is no known sale of the drug in any developing country unless it has been prescribed and obtained with special import licences, by private practitioners.

I share the *British Medical Journal*'s concern that explosive marketing of this kind makes no sense, and that 'the conflict between commercial pressures and medical priorities will need to be resolved' – probably by extension of patent life. Lastly, the *British Medical Journal* cryptically remarked that 'unlike a washing powder, newness should not be seen as a virtue in a pharmaceutical product, and indeed the critical need is for doctors to think more carefully before prescribing a new or newish drug' and that the doctor should not be overwhelmed by hordes of salesmen and television, press and radio advertising.

It is for thinkers in the pharmaceutical industry to come up with an answer to the problem of how to avoid such pitfalls. My only plea is: please be expeditious about the reporting of any pitfalls that a new drug might introduce, and please keep the WHO informed.

The second recent example where pressures built up on the Organisation

was the ordinance on drugs promulgated in a developing country. An expert committee constituted by the national government was formed under the chairmanship of a distinguished Professor of Medicine. The purpose was to examine the pharmaceutical products available in the country and to draft a national drug policy, keeping in view the health needs of the country.

The expert committee set down criteria for the evaluation of all registered and licensed pharmaceutical products manufactured and/or imported into the country. Approximately 2,000 drugs were removed over a period of time from the market. I understand from a telex that I recently received that 41 drugs under the various categories which were removed earlier have been restored by an amendment of the ordinance.

The expert committee's recommendation of 150 drugs for general use in the country (36 of them for primary health care and 100 drugs for import, 77 of which have been identified, with a clause that more will be identified as new drugs become essential to the country's health care) were all approved by the supreme authority in the country. The list approved by the national expert committee closely parallels Technical Report Series No 641 of the World Health Organisation, and the action taken was a perfect example of a national will to start setting the house in order in the pharmaceutical sector.

However, there were some sections of the pharmaceutical industry which went into a paroxysm of flutter, and the country in question, one of the least developed countries in the world, with one of the lowest per capita incomes and which still spends US$100 million on drugs, is told that it has no business to set its house in order. However, very fortunately, good sense ultimately prevailed and the ordinance was in some way modified, so that both the legitimate objections of the pharmaceutical industry and the national health problems were taken into cognisance.

Although we were under enormous pressure, we had to keep quiet on the issue since it is not the role of the Secretariat to comment in public on the policy of any of its Member States, unless requested to do so by the government concerned. However, when the Director-General addressed the relevant regional committee, which happened to be hosted by the country concerned, he took the opportunity of congratulating the government on its courage in starting to put its drug house in order along the lines recently approved by the World Health Assembly, and offered the government WHO's help if it so desired.

I have quoted these two examples to show that WHO is not the animal that is described by Kenneth Adelman in his recent article in the AEI journal on 'Government and Society' entitled 'Biting the hand that cures them'.

The Organisation's activities in the field of drugs and biologicals had their origins in the Health Committee of the League of Nations in 1921 under Sir Henry Dale, FRS, and Professor Madsen of the State Serum Institute, Copenhagen, which resulted in the establishment of a Permanent Commission on Biological Standardisation. Even during the Second World War three important substances were established as international standards – vitamin E, heparin and penicillin.

The first session of the Expert Committee on Biological Standardisation took place in 1947, during the tenure of the interim commission, and one of

the first acts of the First World Health Assembly was to regularise this Expert Committee. Only a few days ago, on 21 September, I had the privilege of declaring open the 33rd session of the Expert Committee on Biological Standardisation, which has met almost once every year. Its agenda this year included the consideration of a revised list of biological substances: over 93 international standards, 102 reference preparations and 165 reference reagents. The first products of DNA recombinant technology are being looked into and one of these – insulin – is already marketed in two countries. The standardisation and control of such preparations, as a result of the Second Pharmacological Revolution, are being carefully assessed. Such modern techniques, as you are well aware, can be the source of hormones, especially where source material is limited.

The reports of the Expert Committees, which appear in the Technical Report Series, contain information on the establishment and disestablishment of standards and reference preparations, with annexes giving requirements for the production and control of vaccines and sera. These reports are therefore regarded as reference sources by many developing countries not having adequate quality control or access to the other information on these substances.

In addition, other biological substances also come under consideration. Last year, for example, we had a meeting on interferon therapy.

Experts come to the Organisation not as members of a government or of a scientific body to which they belong, but as individual scientists. All non-governmental organisations in official relations with the World Health Organisation in any specific field may be invited, and these individuals make very valuable contributions towards the formulation of the reports.

In the pharmaceutical field, our history dates back to 1866 when Jean-Baptiste Dumas was the first to recommend the unification of pharmacopoeias. In 1902 a first attempt was made by several countries to set up an international pharmacopoeia under the Brussels Protocol. In that year, an Agreement for the Unification of Formulae of Potent Drugs was prepared and this was ratified by 19 countries in 1906. The Brussels Agreement was drawn up in 1925 and ratified in 1929. In 1937 the Health Organisation of the League of Nations set up a Technical Commission of Pharmacopoeial Experts which, in 1948, was succeeded by the WHO Expert Committee on the International Pharmacopoeia and in 1951 by the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The Pharmacopoeia is now in its third edition. The publication of the Pharmacopoeia is a mandate to the Organisation as a result of a resolution adopted by the Third World Health Assembly.

A second important function of the Organisation is the expressed wish of the World Health Assembly to recommend international non-proprietary names (INN). In this field WHO has played a leadership role. Its role of devising generic names has been taken over by national commissions, particularly in developing countries, which carry out the acceptance of the names through the pharmacy and drug regulatory authorities. It is our sincere hope that within the next five years all major reference works and medical textbooks and national legislative bodies will accept and implement the INN. The WHO *Chronicle* regularly gives a complete list of names recently recommended, with a request for comments before final acceptance. Four

months are permitted before acceptance is finally given.

In addition to these important activities, WHO recognises that in the present context self-sufficiency in quality assurance is almost exclusively within the grasp of the economic North. If there is any meaning in this international organisation, there must be assistance to importing countries. This is attempted by a certification scheme for pharmaceutical products moving in international commerce by which importing countries can (a) obtain assurance that a given product has been authorised to be placed on the market in the exporting country; and (b) obtain assurance that the manufacturing plant in which the product is produced is subject to inspection at suitable intervals and complies with good manufacturing practices as recommended by WHO.

Only 89 of the 158 Member States have agreed to participate, and even participating countries, because of the nature of the operations in the pharmaceutical sector, do not necessarily comply with the first recommendation by producing a product in a country where it is permitted for local use. Awareness even of this scheme, with all its imperfections, is poor, probably because of lack of understanding. Not all importing countries understand that the certificate does not come automatically but has actually to be requested. These loopholes, if tightened, would certainly increase the effectiveness of the scheme. It is often contended that the developing countries are the hunting grounds of the pharmaceutical industry for proving the merits or demerits of its products. The depot-medroxyprogesterone acetate (DMPA) example need not be overquoted. However, in spite of the fact that more than 80 countries use it in their family planning programmes, it is still a matter of debate, particularly because two influential countries have not approved it for contraceptive use. WHO has, over the past decade, addressed itself to the safety and effectiveness of long-acting injectables both by undertaking clinical studies and by assessing all existing human and animal data. At a recent consultation held in Geneva, it was concluded that DMPA is safe for human use and is an important option for women desiring a method of fertility regulation.

A certificate alone cannot and would not, of course, guarantee the quality at the periphery and at the primary health care centre where the drug or the vaccine has to be used. I am sure you must all have heard of the measles vaccine tragedy which occurred very recently in a large developing country. A well-meaning Rotarian club in another country donated a million doses of measles vaccine manufactured by a reputable leading manufacturer of the vaccine. Because of a probable break in supervision, particularly at the time of administration, two children died and 23 developed staphylococcal septicaemia – obviously a contamination at the periphery. Stories can be spun out of this episode, but the Organisation knew the cause, and an epidemiological investigation is in progress to prevent a recurrence of such episodes.

Adequate information on safety and efficacy is vital, because of the global dimensions of an adverse reaction – SMON in using clioquinol; retinopathy with chloroquine; incipient brain damage in using hexachlorophene; aplastic anaemia in the amidopyrine group of drugs and chloramphenicol; the misuse of combination antibiotics; the rapid development of antibiotic-resistant strains of bacteria; the widespread nosocomial infection

in many hospitals in many developing countries because of poor guidance in the use of antibiotics. All these matters add urgency to the transmission of knowledge to all Member States, the confidentiality of information received being preserved.

Three basic activities are concerned with drug safety and they are delineated in the 1962 resolution of the World Health Assembly: the establishment of minimum basic requirements and standard methods for pharmacological evaluation of pharmaceutical preparations; securing a regular exchange of information on the safety and efficacy of such products; and the prompt transmission to national health authorities of new information on serious side effects.

It is important to have harmonisation of efforts and projected requirements with regard to the safety and efficacy of drugs, post-registration surveillance of their performance and adverse reaction monitoring. It is essential that there is a free flow of information relating to these matters from the developed to the developing world where many countries do not have the wherewithal for collecting such information.

To conclude on a bright note, I believe that a new climate of understanding has developed between the pharmaceutical industry and the World Health Organisation. If this trend can be maintained in succeeding years, we need not fear one another.

Discussants

Dr STUART WALKER
Centre for Medicines Research

We have listened to three excellent papers which have addressed the problems facing the regulators today and what it is anticipated will be the issues in the Second Pharmacological Revolution. Before I comment on these, may I mention the problems facing the regulated pharmaceutical industry as it moves towards the 21st century, and this will provide a backcloth against which to consider the role of the regulators.

If we examine the trends concerned with new drug development over the past 20 years, four principal developments become apparent. First escalating costs, with world-wide research and development expenditure in the pharmaceutical field in excess of £4,000 million, the cost of developing a new chemical entity is estimated at between £30 and £40 million. Second, increasing development times, with 10–12 years often elapsing from the filing of a patent to the marketing of a new chemical entity compared to 2–3 years in the 1950s. Third, an increasing number of safety studies, with toxicological tests being easier to perform than to interpret, and tests often being added to the regulatory requirements before they are fully validated. And, fourthly, increasing animal requirements, with longer-term studies, recovery groups and larger sample sizes, and the repetition of the same toxicology for certain countries.

Along with these changes there are trends which are decreasing. Thus the number of new chemical entities being introduced onto the world market has declined by more than 50 per cent since the early' 60s. The amount of money expended by companies on innovative research, expressed as a percentage of total research and development costs has declined significantly. The number of research based companies marketing new chemical entities has decreased. And, finally, the effective patent life has been eroded away over the past 20 years.

It would be a mistake to suppose that regulations were the only or even the major cause of these changes. Clearly no single factor is solely responsible for the decline in innovation, the increase in costs and other attendant problems. Nevertheless, regulations seem to stand out as a dominant cause partly because their influence on innovation is so direct and powerful. With regard to the pharmaceutical industry, there are regulations that control every stage in the development of a new medicine. There are regulations that control the data requirements necessary before a drug may be studied in man, and good laboratory practice affects the way we carry out those studies. There are regulations which are concerned with the way clinical studies are carried out (good clinical practice), whether drugs are on an approved list or not, and the terms of reimbursement. There are regulations concerned with the review of licences and considerations as to whether a medicine should be allowed to stay on the market. There are regulations that affect the advertising of drugs, the volume, cost and extent of promotion. The last two decades have seen over regulation become an accepted way of life.

What are the answers to these problems? Can we reverse the trends? It

has been suggested that in securing the answers to these problems, the following should be considered:

1 A critical examination of toxicology testing.
2 A radical alteration in the procedures in some countries so that approval times can be reduced.
3 The international acceptance of foreign data.
4 A comparison of drug regulatory authorities approval and rejection decisions to see where they differ and why.
5 A continuing process for evaluating the impact of laws and regulations on the search for new medicines and thus on public health. These will include cost benefit analyses of new regulatory programmes and the monitoring of therapeutic progress under different regulatory regimes.

However, if we are looking for regulatory changes and improvements, we must first decide what causes those changes. Among the major factors causing regulatory change are the following:

1 Drug disasters.
2 Economic pressures.
3 Public pressures.
4 Scientific advances.

But history should not be our only guide to the development of regulatory changes. The question that we have to answer is what does the future hold? Can we, or indeed should we, evolve regulatory approaches that are uniform from country to country? With the vast differences in regulatory systems that are observed from country to country can we expect a system for all? A system that might be right for a developed country such as the United Kingdom or the United States may be wrong for an emerging nation of the Third World. As we enter the Second Pharmacological Revolution should we develop international drug regulations that will satisfy all? What prospect is there for harmonisation and mutual recognition?

If we are to begin a revolution with regard to regulatory changes we have to ask ourselves a number of questions:

1 What precisely do we want the system to accomplish?
2 In what way is our present system deficient?
3 Can those deficiencies be remedied and how?
4 Do proposed changes have any reasonable chance of improving the present state of affairs?
5 What will be the economic costs and the total impact of any changes?
6 How will the proposed changes be evaluated?
7 Will the changes be revoked if shown to be unwise, or not cost effective?
8 Are we estimating the benefits of drugs as well as their adverse drug reactions so that the valuable cost benefit assessments can be made?

I believe the future of any revolutionary regulatory changes must depend on the tripartite collaboration of government, industry and the practising physicians. These three groups are interdependent, and they must communicate, collaborate and interact with one another. Alternatively they can be described as the regulators, the innovators and the investigators. The mandate should be to join in partnership to achieve solutions to the drug problems together in the next 10 years as we enter the Second Pharmacological Revolution.

There are four major areas that demand consideration, and interest me in particular, and for which I hope the Centre for Medicines Research will provide new knowledge.

1 *Animal Toxicology*

A critical evaluation of the rational basis for the animal toxicology carried out prior to the clinical evaluation and marketing of new compounds is essential. There are two important questions that need to be answered:

a How many data and for how long should studies be carried out in animals?

b What is the predictive value of animal toxicology?

The stage has now been reached when it is essential to address these issues, the alternative is the unacceptable one of continuing to apply existing tests uncritically and adding new ones without adequate evaluation.

2 *Trends in New Drug Development*

The evaluation of factors affecting the development of new medicines including the influence of changes in data requirement and regulatory procedures.

3 *Post-Marketing Surveillance*

There are a number of aspects of a drug that are not adequately defined prior to marketing. Various methodologies for PMS are being examined at the present time and it is important to have a system which will adequately alert and assess adverse reactions of medicines. However, it should be considered as to whether an effective PMS system could replace rather than add to the present regulatory requirements with respect to some animal and human studies prior to marketing. To date there is evidence that points to the need and importance of spontaneous and voluntary reporting systems and we should seek to find ways of improving these schemes before instituting new PMS systems.

4 *Benefit Risk Analyses*

It is in no-one's interest to release medicines that are 'unsafe'. However, safety cannot be assessed in absolute terms, it is a risk benefit analysis. During the Second Pharmacological Revolution we should improve our methodology in making these risk benefits assessments.

The research based pharmaceutical industry does have a future as it has proved to be the best method of providing therapeutic advances. The Second Pharmacological Revolution may well begin because of the increase in knowledge and understanding of pharmacological mechanisms. However, this revolution can only become effective if new drugs are developed and regulations must aid the revolution instead of preventing it. There is a need to continually review the scientific data and our regulations, particularly those requiring change.

Revolutionary measures are necessary for the Second Pharmacological Revolution. It is suggested that these should be as follows:

1 A revision of drug regulatory authorities regulations, including data requirements and procedures.

2 A replacement of some animal and human studies with post-marketing surveillance.
3 A revolution in education; public and politicians need to be re-educated to accept and appreciate that no drug is entirely safe and that acceptance of complete safety will mean the abolition of effective medicines.

Dr WILLIAM WARDELL
University of Rochester, USA

We heard yesterday of the dazzling increase in basic biomedical knowledge that can justifiably be described as a Second Pharmacological Revolution. This new knowledge ought to be yielding improved new drug therapies; but we need to enquire whether we have a system of drug development and regulation that will allow tomorrow's discoveries (or today's or even yesterday's) to be translated efficiently into new medicines.

I believe that the application of pharmacology is not keeping pace with the new discoveries, and that unless efforts are made to understand and correct the situation, we will be very disappointed at the results. In this paper I shall present some of the evidence I have for this belief.

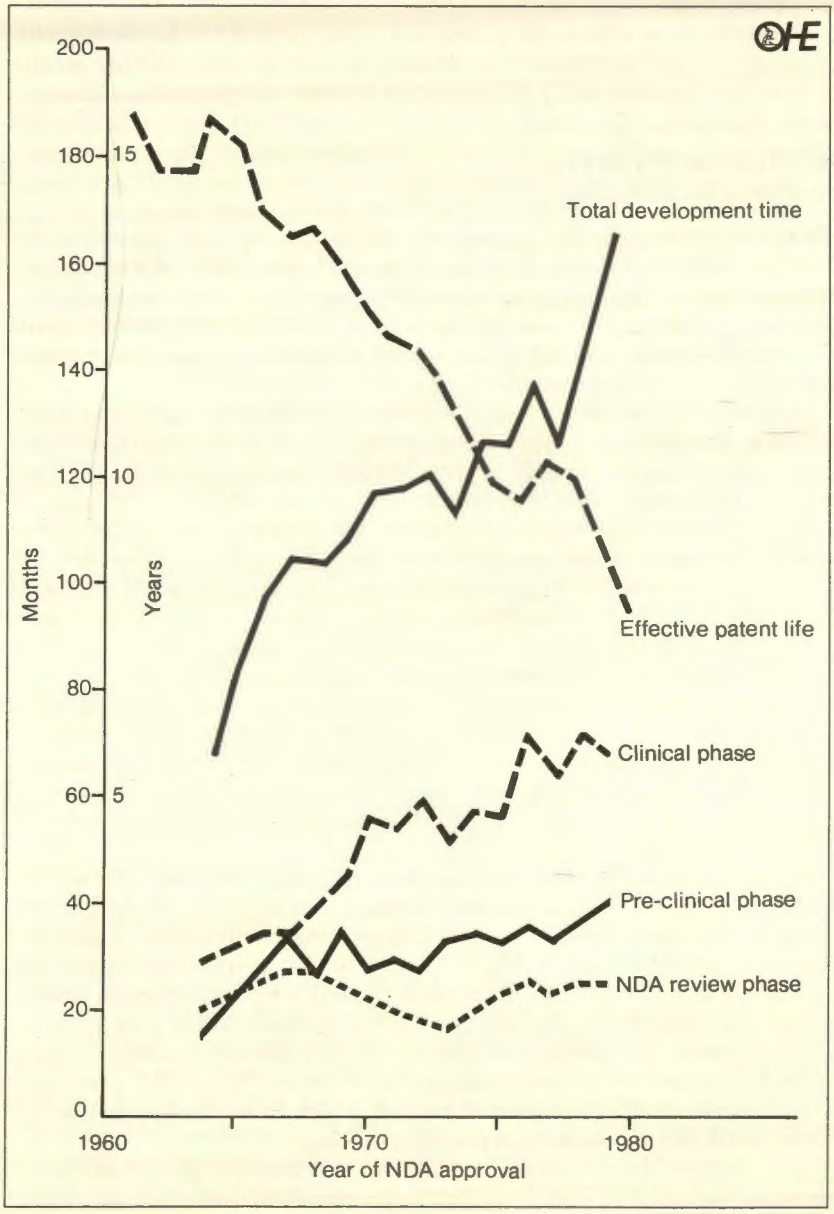
One important reason is the enormous cost, time and complexity of the process. Estimates of the cost now range from $70 million to $100 million for each project that yields a successful new drug to the stage of approval for the market. The scale and complexity is illustrated by the attrition rate of compounds at the various stages of research, reflecting the number of molecules that have to be studied in order to place one on the market. Perhaps 5,000 to 10,000 molecules must be studied in some way to yield one successful marketed product. Approximately ten of these reach the stage of human investigation; five are discarded in the first year thereafter, and one survives the clinical investigation stage to be submitted to the regulatory agency. This one molecule is nearly always approved for the market eventually.

Figure 1 shows how the time required has increased over the last 20 years for all new chemical entities receiving NDA approval in the United States. In the early 1960s, it averaged approximately five years from synthesis to approval of a new drug. The time required has increased greatly in the intervening period. The pre-clinical, clinical, and overall development times have more than doubled. (Based on medians, which give a more robust estimate, the time is even longer – 16 years for all NCEs, and 13 years for self-originated molecules sponsored by US-owned firms. The 3-year difference is due to drugs originated abroad, which have a longer period of clinical work carried out abroad prior to IND filing.)

Since most of the development time happens after the patent has been issued, the increase of eight years in the development time since 1963 must necessarily cause a decline of eight years in the effective (or remaining) patent life; such a decline did actually occur, as is also shown in Figure 1.

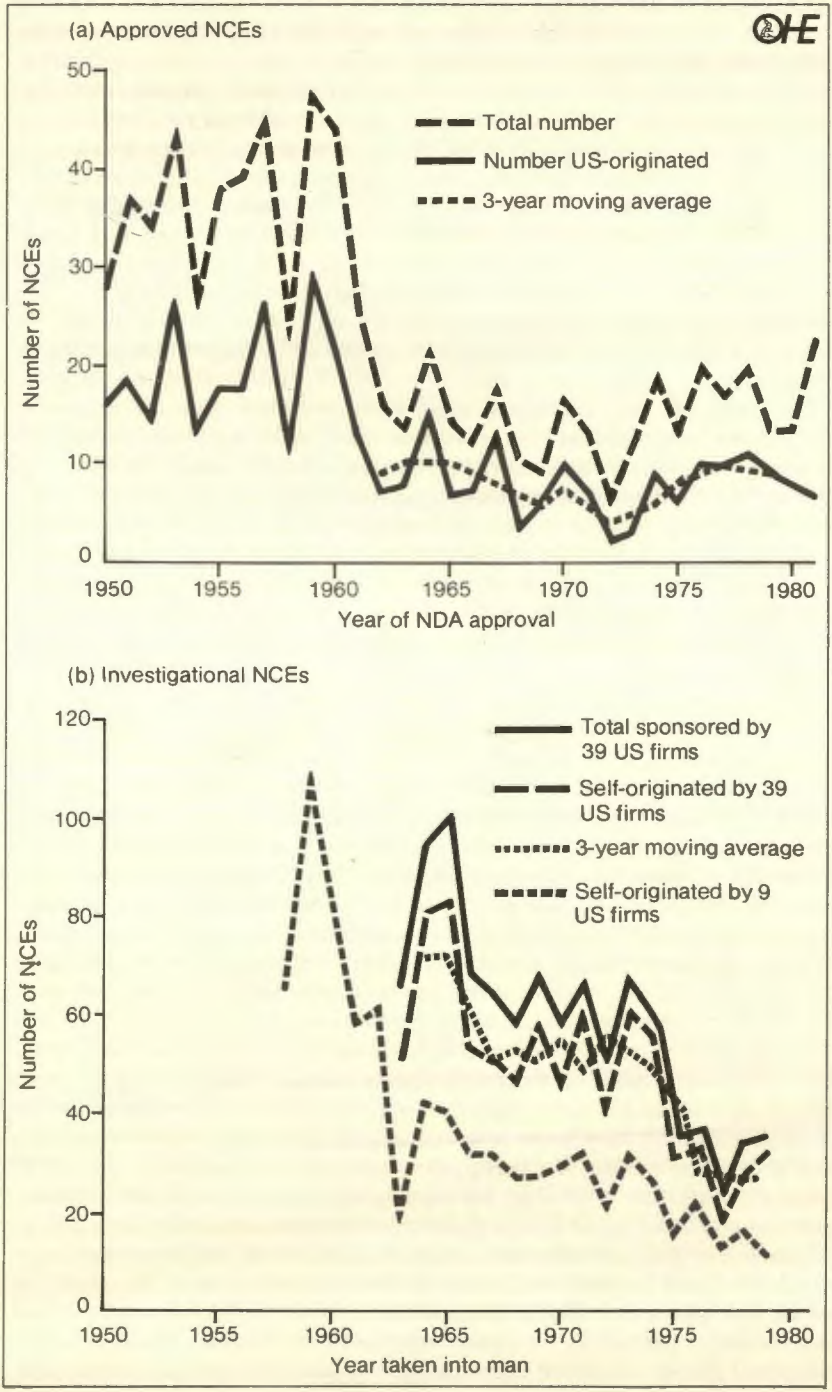
Fewer drugs are now being studied: Figure 2 shows the strong decline that has occurred in the number of NCEs entering human investigation (Figure 2b), and, subsequently, receiving approval for the market. It was well known that around the year 1962 the number of drugs receiving NDA approval declined greatly. We have recently found that there was also a

FIGURE 1 **Development time of US marketed drugs**



steep simultaneous decline in the entry of NCEs into clinical investigation. As the figure shows, this measure of investigational drugs examines the stream of drugs some eight years before they will reach the market, and in a volume eight to ten times the number that will actually reach the market. Furthermore, it can be seen that, after a decade of approximate stability from the mid 1960s to the mid 1970s, there was an additional decline of 50

FIGURE 2 **Numbers of investigational and approved US NCEs**
a) Approved NCEs b) Investigational NCEs



per cent in the number of self-originated NCEs entering human investigation. This new decline started in 1975 and persisted right through to the end of the 1970s. Based on the correlation that can be observed in Figure 2 between the decline in the number of investigational compounds in the early 1960s and subsequent shortfall of new molecules reaching the market over the next decade, I would predict that unless some compensatory factors occur there will be a further decline in the number of new self-originated drugs reaching the market from the US pharmaceutical industry for the rest of the 1980s.

What compensatory factors could appear? One might be a change in the ultimate success rate of compounds entering clinical investigation. It could even turn out, for example, that the decline in drugs entering clinical research is simply a sign that the Second Pharmacological Revolution has resulted in such increased accuracy that we are now discarding drugs that will eventually fail, even before such drugs reach the stage of human investigation.

The study of this important topic is so primitive that there are no industry-wide figures available on success rates, so we have recently looked at some preliminary measures. We divided all new molecules entering research in the United States since 1962 (when the IND requirement came into effect) into cohorts by year of first clinical testing, and analysed the observed success rates – ie, the proportion that actually reached the stage of NDA approval after various time intervals. The answer from our observations is that the observed success rate did rise slightly: from the 1960s to the early 1970s the success rate of those NCEs entering clinical research rose from 8 per cent to 10 per cent.

But what we would really like to know is the success rate of those NCEs that entered clinical research in the 1970s. We cannot directly observe the success rate of these, however, because not enough time has elapsed. The best we can do is to make a model of the process and extrapolate from it to make predictions. Our statisticians helped us by constructing a model that includes the interim data on failures. This work is still in progress, but it suggests that the success rate may be rising to perhaps 19 per cent by the year 2000 for those NCEs that enter research today. Of course, this assumes that existing trends will continue. It cannot take into account further scientific or regulatory changes that might indeed compensate for the decline in compounds entering investigation, but its effects would not be fully seen until the next century.

What can be done to improve the translation of new pharmacological knowledge into useful medicines? In the two days of this meeting, we have heard suggestions for controlling the barriers and for improving incentives to innovators. We now know of practically all the things that *could* be done to improve the system; few really new items are being added to the list. In some countries the regulators are doing their best to remove the barriers, and the pharmaceutical industry trade associations are doing their best to obtain better incentives for innovation. But behind all this there is a larger need that goes beyond regulation, economics and science: the need for education. Education of ourselves, of the medical profession, and even of the industry, concerning the problems and the solutions that have now been set out for us. More importantly, we must educate the public and,

within the public, sick patients, about what the problems are and about the range of solutions available. It is the patients in particular, and the public in general, who now and in the future will control the incentives available to industry and the method of regulation used by government.

I believe that an informed and fully educated public – a public that knows about the Second Pharmacological Revolution, about the doubtful prospects for its implementation, and about the incentives and barriers – is essential if we are to create a system that will allow efficient translation of the knowledge produced by the Second Pharmacological Revolution into practical new medicines.

PROFESSOR PETER TEMIN
Massachusetts Institute of Technology, USA

I want to set Dr Hayes' reforms of the FDA procedures in a little historical perspective. Referring to Professor Teeling Smith's introductory remarks yesterday, I should like to see what light we can shed on the regulation of the Second Pharmacological Revolution by what we have seen in the regulation of the First Pharmacological Revolution. It may help in understanding that history if I introduce a few terms from stochastic decision theory because, as Dr Myers was saying yesterday in a somewhat different context, the process of using drugs and medicine is a stochastic process.

The value of this process is to recognise that there are a variety of risks in the use of drugs, and I want to distinguish between type 1 errors and type 2 errors. In trying to decide whether an hypothesis is true, there are two different risks. One is the risk of rejecting a true hypothesis – a type 1 error; the other is the risk of accepting a false hypothesis, and that is the type 2 error.

In the present context, the type 1 error would be to reject a drug, that is, to keep a drug off the market, that should be on the market, whereas the type 2 error would be to approve for marketing a drug that should not be available for general use.

What are the costs of these different errors as they apply to drugs? A type 1 error – the non-availability of a drug that should be available – increases the risk that sick people fail to recover. A type 2 error has two costs. One of these impinges on the safety part of the regulations: it increases the risk that well people get sick, or that people with one disease then contract another disease or condition through an adverse drug reaction. The second cost of the 'inappropriately' available drug, through the efficacy provision, is the increased risk that sick people fail to recover – they take a drug that is thought to be effective but is in fact ineffective.

The question is how one would estimate the size of the different costs. The type 1 error – the risk that sick people fail to get well – could be estimated from the incidence and prevalence of disease in conjunction with some reasonable estimate of the efficacy of the drug. The type 2 error – making available a drug that should not be available – is much harder to evaluate, because it depends critically on how people act, that is, how people treat the available drug. If everybody knows about drugs and understands the risks and the advantages, the costs are really very small, because people do not use drugs inappropriately. On the other hand, if people –

that is to say, both lay people and medical people – are uninformed, there are potentially large costs.

When people look at what has happened, how will the costs be seen? The type 1 error – the non-availability of drugs – tends to be seen by physicians in such a way that they will put forward a rather general abstract argument about the value of the drugs and the value that would come from having them. The costs of the type 2 error, however, tend to be expressed in a much more dramatic form. If there has been an adverse drug reaction – and particularly where there has been a fatal one – very dramatic stories came to the surface. If we try in an economic sense to weigh the different lives of different people – which is perhaps conceptually and even morally an impossible task – we might say that it is more important to cure many sick people than to run the risk of harming one well person. We may or may not be able to make that an effective economic argument. As a political or social argument, however, even if only a very small number of people can be seen to have been harmed, the costs of the type 2 error seem to be very high. Consequently, people have worried more about type 2 errors than about type 1 errors.

Within that context, let us recall the reaction to the First Pharmacological Revolution in the United States. As the new antibiotics and other drugs became available in the post-war period, there was confusion and concern. There was a sense that there was a need to have some government control of the distribution of the drugs and then subsequently of the research that led to new drugs. Sir John Butterfield has commented on the important role of the Thalidomide tragedy in this process. It is important to note that the impetus for reform had started earlier through the general question about the new pharmaceuticals, although the movement for reform had weakened and was perhaps moribund by the time of that tragic incident. What were the things that had happened?

First, the distinction between prescription drugs and over-the-counter drugs, which was a regulatory reform in the United States that just preceded the First Pharmacological Revolution, was, in the years after the Second World War, enormously extended, and we developed the two-class system of drugs that we know today.

Secondly, the new drugs were shown to be patentable, starting with the streptomycin patent, so that the firms introducing the drugs could acquire property rights.

Then there were the 1962 drug amendments, transferring some of the responsibility for the use of drugs from the doctors and the practising physicians to the FDA. There also were the reforms in the IND, taking that responsibility on to the FDA to some extent.

The 1970 regulations about safety and efficacy further mandated the use of clinical trials to determine the safety and efficacy required by the 1962 laws. Finally, throughout that whole period, there was an enormous expansion of the Government's support for medical research of all sorts.

Most of the reforms were designed to deal with the type 2 error – to make sure that we do not let a drug on the market that should not be on the market. Those are the changes that took place in and by the FDA.

The changes that took place to decrease the type 1 error – the patentability and the government's support for research – were outside of the FDA.

It is a little early to say, but in the Second Pharmacological Revolution we have seen a few things in the United States. The reaction to recombinant DNA – the regulation of the research – was introduced very early in the United States, not just at the national level but in the rather small city of Cambridge in Massachusetts in which I reside. There was a lot of political discussion and some regulation of the research. It was undertaken as a result of a variety of horror stories – or rather prospective horror stories – that turned out not to be true. Consequently, there has been some degree of relaxation.

The patent protection has been extended from the first wave of pharmaceuticals to some of the micro-organisms that are important in the Second Pharmacological Revolution. On the other hand, the research support, which was talked about yesterday afternoon, has been decreasing.

It is a little too early to see exactly where the regulations will go. In particular, we have the question whether there will be a disaster such as the Thalidomide tragedy which would take a small regulatory impetus and convert it into a major one.

At the very time when the regulations in the city of Cambridge were to allow a recombinant DNA research facility to be transformed into a large-scale manufacturing facility, it was reported in the newspaper that someone had washed some manipulated *E.Coli* down the drain into the sewer system. There are lots of folk-lore stories in America about alligators in the sewers in New York, and there are supposed to be some dangerous *E.Coli* in the sewers of Massachusetts. However, nothing seems to have happened and we lived through that!

The conclusion is that the FDA has emerged as the agency in charge of type 2 error. Its function is to keep, in theory, some existing drugs off the market. It is to minimise the type 2 error. Its function is not to discover new drugs.

The reforms outlined by Dr Hayes speak, however, to type 1 error. The aim is to try to make available drugs that should be available. The problem is whether by decreasing the type 1 error the type 2 error will be increased. It would appear that there will not be a trade-off. On the other hand, should there be a tragedy, it will be seen as a trade-off. Even without that, given that the function of the FDA has been to minimise type 2 error, there may be some public discussion suggesting that the reforms introduced by Dr Hayes will increase the type 2 risk. I hope that will not happen, but it is a risk in the kind of reform that Dr Hayes has undertaken.

GENERAL DISCUSSION

As a consequence of Dr Hayes having to depart from the meeting before the general discussion period, questions from the floor concerning his paper were heard immediately after his presentation. These comments and his responses appear first in this record of the proceedings. They are followed by a summary of the discussion stemming from the two other papers given during the fourth session of the symposium.

Mr M. Barlow (Smith Kline & French – International) sought Dr Hayes' reaction to the increasing use of the data contained in the Summary Basis for Approval (SBA) document in a competitive sense and suggested that the

SBA should be required to be written in a way which only provides general information, thereby minimising the advantage gained by competitors obtaining access to the submission. In response Dr Hayes acknowledged that the issues surrounding the nature of the information required and to whom and in what form it should be made accessible presented very real dilemmas. On the one hand it must be recognised that 'trade secrets' exist and that there is competition in the market-place for approval as well as in other respects. Yet, on the other hand, it would be extremely difficult in the United States 'to keep hidden evermore information on which approvals are based'. There is obviously a need to protect companies who have submitted data but this has to be balanced against important 'freedom of information' considerations.

Continuing with the same theme Sir John Butterfield enquired whether companies were informed about the data the FDA proposed to release. Dr Hayes first reassured the audience that a lot of information is protected through the Trade Secrets Act and even under the Freedom of Information Act. He then noted that there is a proposed Bill in the US Congress that would make more specific the mandate that a company should be informed of the information it is proposed to release and that some reconciliation between companies and the authorities should be attempted to achieve a consensus.

Dr Hayes also reiterated the point he had made in his paper that the number of requests from companies for information under the FOI Act processed each year required him to allocate 130 employees to this work, thereby consuming resources from his budget which might otherwise be channelled into the drug approval process.

Replying to a further question from Sir John Butterfield, Dr Hayes commented that in general the response to the programmes in drug approval described in his paper had been favourable. In part this reflects the fact that the FDA task force reviewing drug approval is comprised of people from industry, independent national and international scientific groups, academia and consumer activist groups as well as clinical investigators and this means that consideration is given to the interests of a wide spectrum of groups which might be affected by any proposed regulatory or procedural changes.

Nevertheless, Dr Hayes conceded that fundamental disagreement persists between different sectors of society. At one extreme, it is argued that the drug approval process is much too slow and that the requirements which directly drive the amount of testing are too extensive. It is also suggested that the criteria of efficacy should be weakened or lessened to some degree. At the other extreme it is claimed that the system is, if anything, too fast, leading in the event of a problem such as an adverse drug effect, to comments that a year or two's further regulatory consideration might have prevented the unfortunate incident. In Dr Hayes' view the latter represents fallacious reasoning from a scientific standpoint, but it constitutes nonetheless another opinion which ought to be taken into account.

Between these extremes there are many people who consider that the process badly needs refurbishing from administrative, management and resource allocation points of view, and that the paperwork involved, the appeals process, and the need for a clear statement on the acceptability of

foreign data, urgently require attention. In addition, there are other issues, such as orphan drugs, breakthrough drug provisions and efficacy criteria being addressed by the FDA that are even more fundamental and may possibly require a change in the law.

Dr A. J. Itschner (Ciba-Geigy AG) then asked Dr Hayes, with regard to the question of facilitating the availability of safe, efficacious and good quality drugs, whether he viewed the role of FDA in terms of the protection of the public or the supply of adequate information. Further, he enquired whether every new drug is required to bring *additional* safety and efficacy.

On the first point, Dr Hayes affirmed that in facilitating the entry to the market of safe, efficacious and high quality products there is no question that the promotion of public health is very much central to the FDA's role. The law is also very clear that the FDA exists to protect the public health as well. Consequently, the FDA would be in violation of the legislation if approval were to be granted to a drug with the notation 'we are not sure that this drug is effective and safe and we are giving you fair warning of this state of affairs in making it available'. The FDA must be convinced, by the best scientific standards of the day, that the drug is safe and effective, that the quality is high and that good manufacturing practices are being observed.

Responding to the second part of the question, Dr Hayes stated that there is no legislative or regulatory provision for comparative efficacy review. A drug does not have to show that in comparison with existing drugs it is more efficacious or safer in order for it to be allowed access to the market. Indeed it is not uncommon for the FDA to approve another beta-blocker or non-steroidal anti-inflammatory drug that science does not appear to claim to be a great breakthrough in the relevant therapeutic class. There may, of course, be some specific pharmaco-dynamic or pharmaco-kinetic characteristics that have particular benefits for certain individuals. It is well known that biological response is such that two drugs which seem identical in everything but perhaps a small part of the molecule will have quite different reactions in different people. Against this background the law demands that the FDA approve a drug if, on its own merits, it is safe and effective.

Trends in innovation, liability for adverse reactions and issues arising from the risks and benefits of medicine usage constituted the three main topics for general discussion following the completion of the formal presentations to the fourth session of the symposium.

Focusing on the first of these, Professor D. G. Wibberley (University of Aston) submitted that the overall decline in product introductions observed over the last 20 years or so principally reflected a reduction in what he termed 'less desirable new introductions' (now standing at about 15 per cent of the level operating in the mid 1950s) and that this trend could in fact be seen as a measure of the success of the regulatory authorities' work.

Dr Wardell conceded that the significant drop in the marketing of new products that happened in the early 1960s was in large part due to the efficacy clause and the elimination of drugs that could not be shown to be effective. This did not, however, detract from his view that the flow of good new drugs on to the market in more recent times has been declining and that this trend looks set to continue in the future. And the cause of this

development, in part at least, in Dr Wardell's opinion, is that drugs do not get on to the market unless they demonstrate some incremental advantage over existing alternatives, even though there is no formal relative efficacy requirement. If this paints a true picture of the current state of affairs, then it would seem feasible to argue that an important element of the innovative process is being stifled. Related to this point, Dr Wardell concluded his comments with the observation – which would attract widespread support – that there is a pressing need for useful measures of the therapeutic value and quality of new drugs.

Following this discussion Mr P. Zweifel (University of Zurich) commented that the regulatory authorities have to some extent assumed liability for the success and safety of drugs and then asked what the consequences might be if that liability were to be shifted back in some degree to the manufacturer. In response, Professor Temin noted that the cost of liabilities to drug companies can be severe and suggested that awareness of these potential costs is one reason why manufacturers 'are not as eager as one might think from some of the rhetoric they generate to decrease the regulation by the FDA'.

Addressing the issue raised by Mr Zweifel more directly, Professor Temin emphasised that the reforms proposed by Dr Hayes do not represent a relaxation of standards but rather a tightening of administrative procedures. If, however, there were to be a relaxation of standards, it would be important at the same time to modify the legal basis for liability. This in turn would have additional consequences to which consideration should be given. Such a development could increase the liability of pharmaceutical companies, generating an added cost to drug research. Yet, as various speakers at the meeting had repeatedly made clear, research costs are already rising significantly. This then raises the question of by whom should these extra costs be borne? If, for example, they are passed on to consumers yet another new choice becomes apparent: should the costs of adverse drug reactions be financed by a tax on drug users or on the population as a whole? Clearly, the issue raises many open-ended questions.

This discussion was concluded by a contribution from Mr J. B. Russo (Smith KlineBeckman) who wanted to emphasise that in the United States a company's adherence to FDA regulations and the existence of an approved NDA do not constitute a defence against liability as might have been taken to be implied by some of Professor Temin's remarks. He referred to the case involving the Cutter laboratories in the mid 1950s in which, following the supply of harmful polio vaccine, the company was unable to employ as a defence previous official batch-by-batch approval for the vaccine. Mr Russo indicated that this would still be the case today although he noted that there is currently a Bill in the Senate which would at least afford a company the benefit of the doubt if it had received FDA approval for the product. In other words, 'the other side' would have to demonstrate that a product's 'defect' giving rise to the observed harm or injury was the result of some shortcoming on the part of the manufacturer.

The final part of the discussion period was given over to a consideration of some of the risk/benefit issues surrounding medicine usage. Both Mr M. J. Buxton (Brunel University) and Dr S. Walker emphasised once again the need for improved measures of the benefits of medicines so that benefit-risk analysis might be better facilitated. The former also raised the possi-

bility that, in the current era of escalating health care costs and finite limits to resource availability, drug cost might increasingly become a significant element in the evaluation process.

The major contribution to the discussion came from Professor D. W. Vere (London Hospital Medical College). He commented that his impression was that the regulators do take risk-benefit considerations very much into account but that it is rarely free of complications. One specific difficulty arises over the question of responsibility for known risks. Thus 'where there is substantial risk and yet it is proposed to circulate the product widely, who will "look after" that risk? Some people say that such decisions must be left to the practising doctors – to the medical profession – but that is not always a satisfactory solution to the problem.'

Professor Vere also commented, in the context of adverse drug reactions, that he found the doctrine of retrospective blame particularly pernicious. The benoxaprofen incident provides a contemporary example of the latter and he expressed the belief that the company concerned could not possibly have anticipated the adverse impact among one specific group of the population (the elderly). Criticism has also been levelled at the company's promotion strategy for the drug but Professor Vere suggested that the manufacturer's position deserves closer consideration than it appears to have been given by many commentators. If a company believes that it has a compound with a profile of action which is likely to confer striking benefit and at least one activity which is probably different from all other compounds in the field, then of course the company will want to make the new medicine available as soon as possible and draw attention to it.

Finally, Professor Vere referred to the need for greater public education about risks and benefits. Few people comprehend the concept of risk – to many it is simply associated with gambling. However, if it is proposed to promote widespread understanding of risk it must be accompanied by a great deal of other constructive information if the potentially negative impacts of such increased awareness are to be avoided.

Pursuing the theme of education, Sir John Butterfield highlighted the difficulties that are encountered in this field from his experience on the Health Education Council. In particular there are immense problems in establishing the appropriate messages to put over to the public. In some ways the very name of the HEC poses a problem in that the people the organisation seeks to reach react against the term 'education'. Another obstacle to greater public responsiveness to health education derives from the lower levels of general education found in the UK compared with other nations. In Britain only 20 per cent of school leavers go on to some form of further education. At the other extreme, the corresponding figure in Japan is 62 per cent.

There is no immediate or straightforward solution to the problem of achieving more successful health education. Sir John Butterfield did, however, suggest that a well-informed media could play an important role in generating greater understanding of the concepts of risks and benefits. Mrs H. R. Brus (Smith Kline & French – International) commented that progress in this sphere will also probably require patients playing a more active role in decision making processes. Thus doctors may, for example, discuss the benefits and risks of a particular treatment with their patients so that the

latter can then contribute to the final choice of therapeutic strategy. Unfortunately, as Sir John Butterfield pointed out, time pressures in the National Health Service are such that it would be impracticable for many doctors to adopt this type of approach with all their patients. In addition, it has to be realised that significant numbers of people simply cannot or do not wish to understand the issues that may surround the use of a new medicine and are quite prepared to leave the decisions that have to be made to their doctors.

Dr Sankaran suggested that the patient prescription insert might provide a useful means of educating patients about the medicines they use. It is certainly a topic that has received considerable attention in both the lay and professional press and arguments both for and against the concept have been well rehearsed. One of the major difficulties, however, is to produce an insert that is intelligible to the public. With this point the discussion period drew to a close having raised many issues which will require careful consideration if the potential offered by the Second Pharmacological Revolution is to be fully realised.

SESSION V

THE SOCIAL IMPLICATIONS

Chairman Peter Cunliffe, *Association of the British Pharmaceutical Industry; Imperial Chemical Industries PLC*

At the risk of appearing somewhat provocative, I suggest that the final session may well bring us closer to reality – to real life, that is – than any previous session. We have concerned ourselves with the technological prospects, the disease conditions to conquer, and the technical chances of success. We have concerned ourselves with the economic challenge: can we fund the expense of conquering these diseases? Indeed, shall we be allowed to fund the expense by people who pretend to know better than us the cost-benefit ratio, or by people who do not understand what is meant by a cost-benefit ratio?

We have also concerned ourselves with the trends in regulation. Should there be longer periods of testing, should there be shorter periods, should there be more or less, or should it be different?

Finally, we come to the social implications which may well result from the Second Pharmacological Revolution, and which in many ways are already with us. It is perhaps a truism – on this sort of occasion we may be tempted to forget it – that nothing really happens in the pharmaceutical industry until a patient consumes a pharmaceutical product. All that goes before is a prologue to this one significant act. The patient is, quite literally, a consumer.

It is of considerable importance to us, therefore, to consider the attitude of the consumer – and not only the attitude of the consumer in the United Kingdom and the developed countries but also the needs and, perhaps differently, the aspirations of the consumer in the less developed countries.

Pharmaceutical products already have, and in the future will increasingly have, a profound social impact. If we do not realise this, and fail to attempt to assess the social implications of our actions, of our revolution, we shall be derelict in our duty of care. Unless we consider the social implications, we shall plunge blindly into a series of situations which will urge others to impose social regulation upon us. Therefore, we shall do well to listen attentively to our speakers.

Consumer groups and the pharmaceutical industry in Britain

David Taylor
Office of Health Economics

This paper has two main objectives. First, to provide an overview of the development of the UK consumer movement and its links with key transnational agencies like the International Organisation of Consumer Unions (IOCU). Second, to provide a framework within which consumers' concerns about medicines and the pharmaceutical industry's concerns about 'consumerism' may be further discussed.

In the limited space available it does not attempt to offer a fully comprehensive analysis. Rather, it begins with just a brief historical analysis of the emergence of the main British organisations active in this field, followed by an equally broad evaluation of the consumer movements' achievements and limitations to date. This introduces some topics of special relevance to health care and medicine usage.

The paper then turns to a consideration of some of the problems involved in communication between medicine manufacturers and the consumers of pharmaceuticals. In its concluding section it looks towards the future initiatives industry might take better to explain its contribution to the welfare of the community and thus to counter, or ideally to anticipate and obviate, consumer criticism.

But there are some initial background points which may usefully be made before the main body of text commences. They relate to the origins of the modern consumer movement and its place in our society.

The process of industrialisation affected communities like nineteenth-century Britain in a number of profound ways. For example, the shift of population off the land broke up old social and family structures. The rich traditions of rural life faded into the anonymity of the modern world, whilst technical advances and new methods of production created a market place filled with a growing range of fast-changing goods. As buying power increased, people were faced with a variety of complex decisions of a type unknown to past generations. These had to be made in a relatively unsupportive environment. And so a demand for new sources of purchasing information, and enhanced systems of purchaser protection, also emerged.

One of the ways in which this need was met in the twentieth century was by the formation of comparative testing organisations, the earliest of which were the American bodies Consumer Research Inc (established in 1929) and the Consumers' Union, formed in 1936. These provided the model upon which the post-war development of European bodies like the UK's Consumers' Association, the core of the modern consumer movement, was based.

The first introductory point to be stressed in relation to the above is that

the evolution of consumerism may be seen as a natural development in the markets of the industrialised Western economies, not one imported from outside or one based on alien, anti-competitive ideologies. Some industrialists seem to equate 'consumerism' with 'communism' and some consumerists may be irrationally hostile to industry. Yet the consumer movement is in fact a child of 'capitalism'. At their best its members work to support the process of commercial competition and so, through technological change, to radically expand consumer choice. Such efforts are clearly wedded to the ideals of the Western democracies.

However, even though the common, indigenous roots of the North American/West European consumer movement should be recognised, a second point is that the governments of countries like Britain, Sweden and Germany have played a much more active role in shaping the expression of consumer representation than has been the case in the United States. Some might see a danger of undesirable state (or in the case of the EEC supra-state) powers forming in this context. But in practice the relative moderation of European as opposed to American consumer leaders suggests that governmental funding has, like governmental involvement in welfare provision, if anything tended to reduce the chances of extreme confrontation between private industry and the consumer movement.

Following on from this, a third point best clarified at the start of any study of consumer affairs relates to the representativeness or otherwise of 'consumerists'. Critics often highlight the fact that consumer organisations are usually joined only by the better-off and better-educated, and that although smaller, radical bodies often claim to be speaking for the population as a whole, they generally have few grounds for doing so. In Britain, for instance, the Patients Association has only some 1,000 subscribers, whilst Social Audit is financed almost entirely from funds donated by charitable and other bodies. There is no mass market for its products.

The view taken in this paper is that such a situation is more or less inevitable. Opinion leaders will always tend to be unusual people, appealing in the short-term to only a small minority of the population. Despite the obvious dangers associated with their gaining excessive power, this does not necessarily invalidate what they have to say. Nor does it mean that consumer activists do not have the best interests of the majority of consumers at heart. Where there is conflict between producers and consumer leaders, self-appointed or not, the former would probably do best to judge any criticisms made against them as objectively as possible in the light of the facts surrounding each case. 'Consumerists' should not be ignored just because they are, like industrialists, members of an elite.

The historical development of the UK consumer movement

Table 1 lists the main events in the development of the UK consumer movement. In the period since the Second World War three key phases of activity can be identified. The first took place in the period 1945–50. During this time of economic normalisation after the war the then Labour Government established a network of bodies the role of which was to represent the consumers of newly nationalised industry goods and services. Although they were of limited value, it is only recently that any significant review of

TABLE 1 **Main events in the development of the British consumer movement 1939 – 82**

Year(s)	*Event*
1939–45	Citizen's Advice Bureaux (CABx) service first established in 1939. British Standards Institution (BSI) becomes closely involved in establishing basic utility standards for a wide range of products.
1946	Domestic Coal Consumers' Council (DCCC) established.
1947	Central Transport Consultative Council (renamed the National Transport Consumers Council in 1978) formed. Regional Transport Users Consultative Councils (TUCCs) provided for in the same Act.
1948	Electricity and Gas Consumers/Consultative Councils set up. In the same year Heathrow Consultative Committee has its first meeting. Subsequently, in 1965, the British Airports Authority was required to establish consultation facilities at all its sites.
1951	BSI forms its Women's Advisory Committee.
1956	The Consumers' Association (CA) is established.
1957	*'Shoppers' Guide'* (BSI) and *'Which?'* (CA) commence publication, The Pharmaceutical Price Regulation Scheme (PPRS) is implemented.
1958	ABPI establishes the Code of Practice Committee to regulate prescription medicine advertising.
1959	Molony Committee on Consumer Protection begins its enquiries.
1960	IOCU, the International Organisation of Consumers Unions, formed by CA, the American CU and the independent consumer bodies of Belgium, Netherlands and Australia.
1962	The first British edition of the Medical Letter is produced – leading to the CA's 'Drug and Therapeutics Bulletin' The Advertising Association establishes the Advertising Standards Authority Ltd. In Europe the Bureau European des Unions des Consommateurs (BEUC) is formed.
1963	In response to the Molony Committee's report the Consumer Council is established. So too are the National Federation of Consumer Groups and the Research Institute for Consumer Affairs. Patients Association formed.
1967	The Sainsbury Commission on the supply of medicines to the NHS reports. It leads to a strengthening of the PPRS.
1968	The Medicines Act enables the establishment of the Medicines Commission at the start of the 1970s
1969	The Post Office Users National Council (POUNC) is formed. In Kentish Town the CA establish the first Consumer Advice Centre (CAC) in the UK.
1970	The Consumer Council is abolished. The Institute for Consumer Ergonomics at Loughborough is founded by CA.
1971	Social Audit Ltd and the Public Interest Research Centre Ltd (PIRC) come into being.
1972	Local government reorganisation contributes to the development of the Trading Standards/Consumer Protection Departments. The first LA funded CAC is opened. Sir Geoffrey Howe is appointed first Minister for Trade and Consumer Affairs.
1973	The Fair Trading Act leads to the formation of the Office of Fair Trading and the associated Consumer Protection Advisory Committee (CPAC). The Price Commission was also set up under counter inflation legislation. A new Airline Users Committee is formed. In Europe BEUC establishes a permanent office in Brussels with Eirlys Roberts as chief executive. The Consumers' Consultative Committee (CCC) is formed.
1974	The short lived Department of Prices and Consumer Protection (DPCP) is created. NHS reorganisation leads to the formation of Community Health Councils (CHCs).

Year(s)	*Event*
1975	Shirley Williams, then Secretary of State for Prices and Consumer Protection, sets up the National Consumers Council (NCC). Similar bodies are formed in Scotland, Wales and Northern Ireland.
1978	The Consumers in the European Community Group (CECG) is created, formalising a loose association of UK bodies established in 1972.
1979	DPCP is disbanded, together with the Price Commission. Mrs Sally Oppenheim made Minister of State at the Department of Trade with responsibility for consumer affairs.
1981	An initiative led by IOCU and BUKO results in the formation of Health Action International (HAI). Dr Gerard Vaughan moves from the DHSS to become Minister of State for Consumer Affairs.

the Nationalised Industry Consumer/Consultative Councils (NICCS) has been attempted.

The second phase of vigorous activity took place between 1956 and 1963. At the start of this economically successful seven-year period the British Consumers' Association was founded. It launched its magazine *Which?* the next year, just after the British Standards Institute first published its short-lived *Shoppers Guide*. Following the report of the Molony Committee in 1962 the original Consumer Council was created in 1963, under the directorship of Dame Elizabeth Ackroyd.

Other significant events in the period included the formation of the Pharmaceutical Price Regulation Scheme in 1957 and the ABPI Code of Practice Committee in 1958. The CA's *Drug and Therapeutics Bulletin*, edited by Andrew Herxheimer and based on the American CU's *Medical Letter*, was first published in 1962, at around the same time as the moves which created the Patients Association took place. Abroad IOCU was, with the help of the CA, established in 1960 and the Bureau European des Union des Consommateurs (BEUC) in 1962.

The third phase may be dated roughly to the years 1970–75. It began as the then Conservative Government closed down the old Consumer Council. Then Local Government reorganisation led to the formation of new LA Trading Standards/Consumer Protection departments, which after 1972 began to open a number of Consumer Advice Centres. Also the Office of Fair Trading was set up by Sir Geoffrey Howe in 1973, whilst a new National Consumer Council (NCC) was formed by Shirley Williams in 1975. Other events in the period include the formal creation of the British Medicines Commission, the establishment of Social Audit, the formation of Community Health Councils and, just before Britain joined the EEC, the entry of the CA into membership of the Bureau European des Unions de Consommateurs.

At the end of the first half of the 1970s all the key elements of the British consumer movement were thus in place. Since then there has been, coinciding with the economic downturn, somewhat of a lull in the sequence of events. Yet this should not be thought to imply that the consumer movement is nearing the end of its useful role. Rather, it may be thought of as undergoing a period of consolidation, prior to a fresh wave of activity.

In the UK this might focus on service provision in general, and the exten-

sion of consumer rights in the sphere of the nationalised industries in particular. There is evidence (NCC 1981) that the latter is today the field in which most people in Britain feel dissatisfied with, and unable to influence, service provision. 'Third world' consumer issues are also likely to be of concern throughout the Western industrialised nations.

In this last context it may be noted that following the successful intervention of the International Baby Food Action Network (IBFAN) in relation to the baby milk controversy of the late 1970s, IOCU has recently helped to establish three similar bodies in the fields of health (Health Action International – HAI), agricultural chemicals (Pesticide Action Network – PAN) and other third world consumer products (Appropriate Products Research and Action Network – APRAN).

The work of the first of these, HAI, is touched on again below, since it involves several British organisations, including War on Want, Social Audit and Oxfam, and also relates closely to the business of pharmaceutical manufacturers. It is today the main sphere of consumerist activity where people in industry fear there is a genuine reason for concern. This is both because of the real problems surrounding health care in the third world, and because groups like HAI, run by activists with seemingly little external control or accountability, might mislead public opinion, and so undermine community interests.

Achievements and limitations of the British consumer movement

The prosperous years of the 1960s and the early 1970s saw many initiatives designed to improve the quality of life for the citizens of all the major Western economies. In Britain, for instance, the passing of the 1970 Chronically Sick and Disabled Persons Act triggered a range of measures intended to improve the support available to physically impaired members of the population. The 1976 Health and Safety at Work Act reflected new concerns regarding the well-being of workers, and legislation on sexual and racial discrimination is a third area in which citizens' legal rights were extended.

To an extent, therefore, the introduction of the 'consumer laws' outlined in Table 2 may be seen as part of a broader social shift generated by a variety of complex forces. Nevertheless, few commentators would deny that the consumer movement played a significant part in this process, and that it was instrumental in forming and promoting many of the legal protections now on the statute book.

In addition, there can be little question that the type of information supplied by the Consumers' Association has been of value to those consumers able enough to employ it during the course of their purchasing decisions. And even just the background presence of comparative testing and allied bodies in the market place has probably caused manufacturers of goods to revise standards. Consumer criticism has increased their readiness to participate voluntarily in various measures aimed at reform. These include the OFT's efforts to encourage industries to, through Trade Associations, develop comprehensive, self-regulated codes of conduct.

Finally, the Consumer Advice Centres, Citizens' Advice Bureaux and Local Authority Trading Standards and Consumer Protection Departments

handle over a half a million complaints a year, according to OFT statistics. To this (minimum) estimate should be added the 70,000 plus complaints/enquiries made to NICCS, and the many other consumer contacts made by independent advisory agencies and, of course, the media. Programmes like *Checkpoint* and *That's Life* have helped to augment the wide network of systems which in the UK can assist individual consumers to find redress when they have been unfairly treated or otherwise harmed.

All this amounts to a very considerable record of achievement by the British consumer movement, which has also been active abroad. Examples of the areas in which it has been involved range from the EEC's concern over car pricing to the world-wide debate on the sale of baby milk. Yet despite its successes, the consumer movement has not been without critics.

One of the latter is an academic commentator, Christina Fulop, who in 1977 published through the Advertising Association a powerful analysis of UK consumerism. (See also Fulop 1981.) She claimed to have identified five basic assumptions often questionably made by consumer bodies. They were:

1 That 'confusion' (ie, complexity) in the market place always affects consumers badly, and that therefore wherever possible the selection of products and choices facing consumers should be minimised and simplified.
2 That consumers have uniform needs and preferences.
3 That advertising undermines consumer sovereignty through enabling producers to manage people's wants.
4 That price rather than quality should be the key consideration in product choice.
5 And that consumer bodies are representative of consumers.

It may not be correct to attribute such naive views to all modern consumerists, or to assume even that those who hold them are always wrong. But Fulop's analysis (which also suggests that many consumerists have a weak grasp of economic theory) indicates that, far from aiding competition and consumer sovereignty in the market place, some forms of consumerism may actually undermine it.

At worst, elitist groups who doubt the capacity of ordinary people rationally to judge their own interests could inspire legislative controls which would undermine basic freedoms, denying individuals the right to buy goods and services of their choice, and stopping producers from stimulating new desires or raising existing expectations. It is vitally important for members of the consumer movement to realise that the modern Western world competition leading to dynamic technical changes (which open up radically new opportunities for consumers) is more important than static competition which just makes existing goods as cheap as possible. In economic terms, consumer interests may in many cases be better served by 'workable' competition between large, perhaps oligopolistic, producers than by perfect price competition between small, non-innovative firms.

Anyone familiar with the pharmaceutical market will see from Fulop's list that many of the areas in which medicine manufacturers are criticised are ones in which other industries also receive adverse comment. The pharmaceutical sector is not 'picked on' especially by individuals concerned with issues like product prices and the effect of promotion, although the

TABLE 2 **Recent UK consumer protection legislation – a selective summary**

Foods and Drugs Act 1955	The first legislation in this area was in 1860. The comprehensive 1955 Act was intended to ensure that food offered for sale for human consumption is clean and wholesome, and that descriptions are accurate. Subsequent regulations based on the Act have extending controls on advertisings and labelling
Consumer protection Act 1961	Enabled the formation of regulations aimed at ensuring the safety of particular classes of goods. Now largely replaced by the Consumer Safety Act – see below.
Weights and Measures Act 1963	Consolidated legislation enacted over the course of a century. It made it a criminal offence to give inaccurate measures/weights, and laid down a wide range of detailed requirements about how goods should be sold. See also the 1979 Act below.
Trades Descriptions Act 1968 (and 1972)	Prohibits the misdescription of goods, services, accommodation and facilities provided in the course of trade and requires clear and accurate pricing. The 1972 Act required foreign goods to be conspicuously so identified.
The Medicines Act 1968	This bought together much past legislation on medicines, including the Pharmacy and Medicines Act, the Pharmacy and Poisons Act and the Therapeutic Substances Act. It created three types of medicines, those available only on prescription (POMs), those obtained through a pharmacy only (PS) and those on the General Sales List. It also radically extended the state's capacity to control the development and marketing of medicines. The considerable new powers conferred on Ministers are mainly expressed via the DHSS, which (contrary to Sainsbury Report recommendations) is the licensing body which permits the trial and sale of new pharmaceuticals. The Medicines Commission, also created by the Act, serves primarily as an advisory body in its enforcement. Its subsidiary bodies include the Committee on the Review of (existing) Medicines, the Committee on Dental and Surgical Materials, the British Pharmacopeia Commision, the Veterinary Products Committee and the Committee on the Safety of Medicines. The latter replaced the voluntary Committee on the Safety of Drugs formed in 1964 just two years after the thalidomide tragedy.
Supply of Goods (Implied Terms) Act 1973	Voids any contract of sale of goods which releases retailers from their obligation to supply goods which are a) of merchantable quality b) which meet the description supplied and c) which are fit for the purpose implied in their sale.
Fair Trading Act 1973	This led to the establishment of Office of Fair Trading and associated bodies like the Consumer Protection Advisory Committee. The envisaged role of the OFT was to inform and educate the public and to control or abolish harmful trade practices more quickly than previously had been possible. The Act also required OFT to administer the Consumer Credit Act.
Consumer Credit Act 1974	This gives consumers protection in credit and hire transactions. Businesses involved in such activity must be licensed and provide information about the true cost of the credit they offer.
Unfair Contract Terms Act 1977	Renders ineffective exclusions seeking to avoid liability for harm caused by negligence. Applies in a variety of associated cases.
Consumer Safety Act 1978	Extends the powers conferred on the Secretary of State for Trade by the 1961 Consumer Protection Act. Regulations currently apply to products ranging from nightdresses and toys to tear gas capsules and electrical appliances. The Act also provides for the banning of unsafe goods and the issuing of warnings about those already made available.

The Sale of Goods Act 1979	This consolidates earlier measures, including sections of the Supply of Goods (Implied Terms) Act 1973. It ensures that buyers have a civil law right to expect that sellers have a right to sell, and that the goods they obtain are of merchantable quality, are fit for their purpose and meet their descriptions. These rights cannot be removed from the consumer.
Weights and Measures Act 1979	This provided for a new system of quantity control for pre-packed goods based on the concept of average contents.
The Competition Act 1980	Strengthened the Fair Trading Act of 1973 by providing for the investigation and control of individual (rather than general) anti-competitive practices and efficiency audits of certain public sector bodies
Supply of Goods and Services Act 1982	Part I of this Act, which will come into effect in January 1983, ensures that consumers who acquire title to goods by means other than purchase or hire purchase, (for example, barter) are protected by the normal implied terms of suitability, merchantability and compliance with their description. Part II provides that, unless it is agreed otherwise, consumers will be able to expect those who supply services to do so with reasonable care, in a reasonable time, and at a reasonable charge. It is questionable whether the latter actually extends existing common law protection, although it is clearly useful in making explicit such entitlements.

Note The above list is not intended to be comprehensive. It excludes many Acts which may be thought relevant to consumer affairs, such as, say, the Insurance Companies Act of 1974, the Air Travel Reserve Fund and the Policy Holder Protection Acts of 1975 and the Estate Agents Act of 1979. But it does give a general overview of legislative developments in the last two decades or so.

prescription medicine market is in some economic senses a special case.[1] It also happens to be one in which safety is a particularly sensitive topic, and one in which direct communication between producers and consumers is unusually difficult.[2] The next section discusses why this is so, prior to a look at some of the ways in which the two sides might in future be brought closer together.

The consumer in the health market

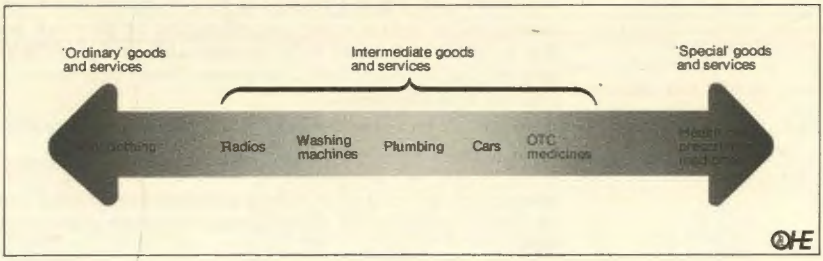
Figure 1 suggests that there is a spectrum of consumer goods and services ranging, in the terminology of this paper, from the 'ordinary' (that is, common commodities or simple products) to the 'special'. Consumers should quite easily be able to appreciate the functions and quality of the former, and so the trading relationships shown in Figure 2 are themselves uncomplicated. Figure 3, by contrast, indicates that in 'special' areas like the purchase of medicines and health care very much more complex arrangements exist. The choices confronting the consumer are so difficult that he or she normally seeks professional guidance.

In the middle of the spectrum are intermediate goods and services such as cars and house repairs or extensions. The purchase of these has often

1 Central government controls manufacturers' profitability and costs in Britain via the PPRS and related controls such as those over promotion outlays.

2 It is assumed that the audience for which this paper is intended understands the strength of the case the pharmaceutical industry in the UK can make in relation to its products' contribution to the economy and the well-being of the community.

FIGURE 1 **The consumer goods spectrum**



been the major concern of consumer advisory bodies like the CA and the CU.

Detailed analysis shows that there are in fact at least four sets of factors which make the health area an archetypically 'special case' for consumers. First, the widespread utilisation of third party payment schemes – whether state/tax or insurance company/premium based – may radically change the consumers' experience of payment. It can promote a false sense of excessive cost in some areas, and lead to an unnecessary acceptance of waste in others.

Second, the 'agency' relationship in health care often transcends the normal producer/consumer one. That is to say, professionals like doctors and pharmacists often take on a dual role as both service suppliers and proxy consumers. This is because many people believe that they simply do not possess the knowledge needed to decide what care they require when ill. They therefore appoint the doctor or pharmacist as their agent or advocate.

Third, following on from the above, the emotional response of a sick person to those providing care is likely to be very different to that of a customer buying an ordinary service from a tradesman. Even informed individuals may need, when severely distressed, to suspend their critical feelings, trusting others to a perhaps irrational degree.

In the recovery period the reverse can occur. As subjects reassert themselves and return to an active social role, they may forcefully reject the

FIGURE 2 **The 'ordinary case' producer/consumer relationship**

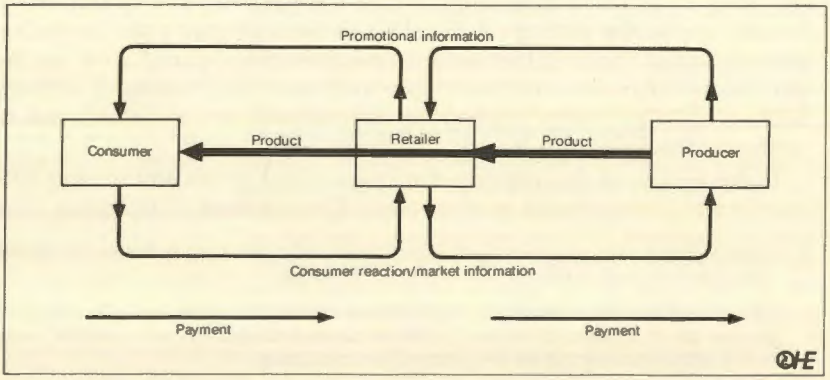
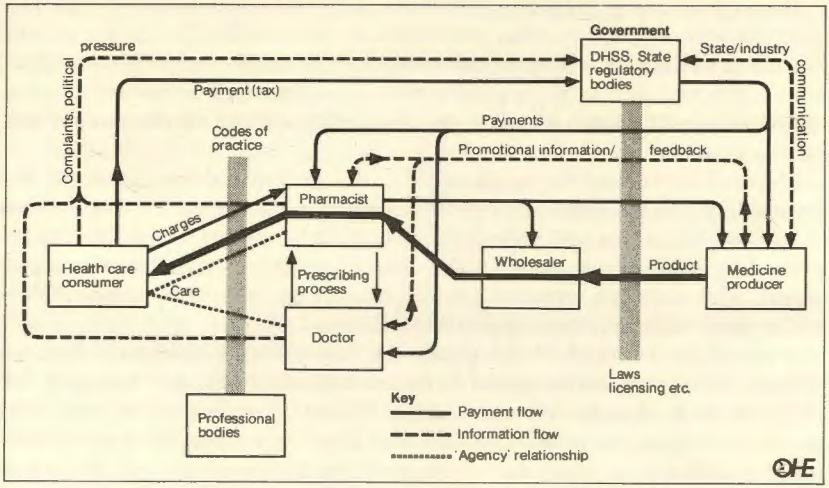


FIGURE 3 **A 'special case' producer/consumer relationship – health care and prescription medicines in the NHS**



people or the treatments which supported them through a period of dependence. Linked to this last is the phenomenon of denial in which people do not wish to recognise the inevitability in nature of disease, pain and death. In reaction they may pay exaggerated attention to events like drug side effects. The implication is that if only doctors and drug makers stopped interfering, life would be perfect.

Finally, the fourth set of forces which make the health care consumption process an atypical one is the unique set of laws and professional and voluntary codes which affect its delivery. The existence, in developed countries especially, of regulatory systems relating to matters ranging from the safety of medicines to standards of professional conduct must mean that the medical market place is a long way removed from the type of simple free market where consumer sovereignty alone acts as a major guiding influence.

Taken together, considerations like these help explain why direct communication between medicine producers and consumers can be difficult. And public debate is further distorted by the limitations of the most generally used means of communication, the mass media. Neither newspapers, television nor radio are well adapted for the accurate transmission of complex, objective material about the use of medicines to the public. Rather, they tend to focus only on simplified messages, usually with an emotive or conflict related content.

It is, of course, precisely these limitations which enable pressure groups like IBFAN to be so effective in gaining sympathetic media coverage. Building on the complex reality surrounding the use of baby milk in the third world, IBFAN members in the late 1970s projected simple messages like 'baby milk kills 10 million babies a year in the poor world' and 'commercial baby milk promotion is the factor responsible for the decline of breast feeding'. A carefully co-ordinated campaign, including a steady stream of messages into the main media gateways from a variety of seemingly

independent sources, soon established the above grossly distorted 'truths' in the public mind and the political arena.[3]

Broadly speaking, Health Action International may intend to do for the pharmaceutical industry what IBFAN did for baby milk. That is, by attacks launched in the rich world, brand companies as mass-murderers or otherwise anti-social, and so apply pressure which is ultimately aimed at bringing the third world pharmaceutical market under a form of 'de-commercialised' control.

It would be beyond the scope of this paper to try to debate in detail the desirability of HAI's ultimate objectives. But what can be said with certainty is that the Western world's medicine manufacturers have a clear interest in defending themselves against false attacks on their record in the third world, and an even greater one in demonstrating their responsibility within, and value to, communities like Britain.

It would be a tragedy if the work of influential HAI participants such as Oxfam, who have unquestionably uncovered some genuine examples of abuse in areas like medicine promotion in some poor countries, were ultimately to undermine public confidence in (and the income of) the pharmaceutical industry to such an extent that the entire process of medicine innovation becomes threatened. The question thus arises, how can industry better communicate with consumers, so as to help them realise the potential value of new therapies, and to dispel false images of the costs of and harm caused by medicines?

Moving closer to the consumer

Some people in the commercial world feel that a good deal of the fundamental blame for public misinformation about medicines and other health related topics lies with the media. Occasionally they, like some politicians, accuse newspaper, television and radio reporters of gross bias, and call for major reforms in the structure of the media. Talk of legislation aimed at 'quality contol' is not unheard of.

But the view taken in this paper is that such proposals are usually impractical or otherwise misguided. They tend to ignore the commercial and institutional realities of the media world, and the political dangers of additional controls on the press. Also, no conceiveable reform of the latter could serve as a 'cure-all' destined automatically to give the public an informed and balanced view of topics like medicine pricing and safety. Although the media sets the agenda for public debate – that is, identifies topics of general concern – its inability to handle or transmit the detailed, complex material essential to any real understanding of medicines means that other communication routes can have a more important effect on finally shaping public opinion.

However, media coverage should of course be of the highest standard possible. The skill of reporters is a crucially significant factor in achieving this, even though careful analysis tends to suggest that often it is influences outside the media that most need reform. Alarmist or otherwise misleading

3 The result was the UNICEF/WHO initiative which led to the WHO marketing code on breast milk substitutes. IOCU has recently been asked to monitor the implementation of this code, and IBFAN members are now active in persuading WHO member states to ratify the code.

stories frequently originate from interested parties which fail to exercise adequate ethical control over their actions.

It may be distasteful even to consider the possibility that individuals, including some parliamentarians or academics, might be prepared to exploit public concern over topics like health and safety just to gain publicity or research funds. Yet such events probably do occur.

In other instances messages may not be transmitted accurately through the media simply because they are not competently presented. In connection with the pharmaceutical industry specifically, it may occasionally be that reporters are blamed for bias when the real failures exist in the way companies themselves handle their relations with the media and/or derive their consumer related policies.

Effective action here may not simply require the employment of staff able enough fully to understand problem areas and articulate enough to put industry's case. Public relations/affairs departments have a potential role far more significant than one confined simply to sophisiticated apologism. Instead, they should perhaps be sufficiently professionalised, despite possible opposition, to feed back information within a company in such a way as to try to ensure that consumers' views and interests are fully comprehended. Without appropriate arrangements, no organisation can be sensitive to current public opinion, still less be able intelligently to anticipate future trends and act to avoid conflicts with consumers.

Examples of areas where better communication, and evidence of industry's good faith, may be needed in the UK include the debates over product liability and the risks of medicines; the question of informed consent in clinical trials; and the particular problems linked to the third world, including those relating to the need for new medicines and raised promotional standards.

The latter are both ones in which consumer movement criticisms of industry clearly have some justification. Yet in the domestic sphere the extent of consumer/producer differences are probably not as great as is sometimes feared. For instance, few people in the pharmaceutical industry would today deny the desirability of obtaining the informed consent of participants in clinical trials of new products. But there is a problem in that not all people might wish to be consulted or be able genuinely to give such consent.

Older people suffering terminal conditions may in principle want to participate in efforts to find effective therapies, especially in areas like cancer where often any hope of cure must rest on experimental interventions. Yet at the same time they might not desire to face fully the reality of their situation, or may simply wish to leave decisions in their doctor's hands. Close relatives may in such circumstances not necessarily be the right people to decide on matters like participation in trials, especially when they might be affected financially by the death of a sick individual.

Younger, better educated individuals, particularly when they have non-fatal illnesses, would by contrast probably feel that they themselves ought to weigh any risks they may be exposed to by a new medicine very carefully against the possible gains. A general point to draw is that different groups of consumers have different emotional, physical and economic needs. What the pharmaceutical industry has to do is to find the most appropriate

ways of imparting information about its products and activities to each subgroup of the medicine taking population.

It would be beyond the scope of this paper to examine the various channels open in any detail. But in concluding it is worthwhile to note four of the more promising producer/consumer contact routes currently open in this 'special case' area, and to mention just some of their positive and negative aspects. They are:

1 Supply of material about health and medical issues via the media possibly by advertising campaigns.
2 Supply of written material with medicine packs. Such inserts may be:
   a) specific to each individual product.
   b) relevant to broad groups of products.
3 Supply of educational aids to doctors and allied professionals like pharmacists, who may employ them in the course of their daily contacts with their patients.
4 Support to patient groups and charities involved with self-help and associated care activities in fields where subjects are likely to be medicine users.

Briefly, the first of these has certain advantages in relation to the general transmission of, say, economic arguments relating to health care and medicine manufacture, and perhaps also to some forms of general health education. But it is limited in as much as this channel is, as was pointed out above, not usually suitable for imparting complex information.

The second should provide a direct channel to medicine users. Research by bodies such as the Rand Organisation in America indicates that inserts are quite frequently read and that drug knowledge is improved by them. They are attractive, in as much as their distribution could be seen to be a step towards meeting the active demands of consumers for more medicine information, and they might indeed be highly appropriate in the context of therapies used by younger, educated and relatively healthy people. Oral contraception is an obvious example.

But across the broad range of the population there is little reason to suppose that PPIs change patient behaviour in any significant manner. Also those who value them could well be able to use alternative information sources, such as *Martindale*, the *British National Formulary* and the many commercially published medicine guides. Practical difficulties surround their use in contexts where there is not original pack dispensing. The cost effectiveness of PPIs must therefore be questioned, particularly as in the near future new computer based information technology could easily revolutionise this field.

From both an educational and economic viewpoint the third option of providing doctors, pharmacists and perhaps other health workers with aids to patient communication looks more attractive at present. Indeed, it is already a widespread practice. Health workers can use commercially supplied material as they think desirable, perhaps giving written information to some groups of patients whilst offering verbal advice and showing simple visual material to less academically inclined consumers.

However, the difficulty here from the viewpoint of some commentators is that this option leaves control of information release firmly in the hands of groups like the doctors.

Additional, rather than alternative, measures to meet this criticism could involve the fourth option listed above, support for, and the supply of medicine related information directly to, self-help groups and medical charities. Once again, many pharmaceutical companies already provide help in this direction. But it may in the future be strongly in the interest of free enterprise medicine manufacturers to enhance consumer awareness and knowledge about drugs via this last route.

This is essentially because the success of the pharmaceutical industry in the West has been based on competitive innovation, albeit within a particularly controlled market place. This ultimately demands, even in an area involving 'special' goods and services like health care, informed consumer participation in decision making, together with the guiding influence of professional agents or advocates.

If the pharmaceutical industry is to survive and prosper in what may well be a difficult economic climate in the 1980s, it must play an active part in helping medicine takers to realise fully the existing and potential future benefits of pharmaceutical treatments, and to balance these sensibly against their risks and costs. If it fails in this, political forces could deprive 'sovereign' consumers of medicines which they would, if they had the opportunity, be prepared to 'vote' for with their money.

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Responsibilities to the consumer

Dame Elizabeth Ackroyd
Patients Association

When I was asked to take part in this symposium, I assumed that I was playing the role of the token Consumer (or 'Consumerist', as people who don't like us describe us) without whom no self-respecting conference these days feels able to face the world. But when I saw the list of speakers and discussants, I realised that the organisers could congratulate themselves on killing two birds with one stone, since I appeared to be the token female as well – until this morning, that is, when it was a pleasure to be joined by Professor Hurley.

However, on reading Professor Teeling Smith's historical background, with which he so felicitously opened the symposium, I found that I was cast in a more positive role: one of a pack of irritable wolves snapping at the ankles of the pharmaceutical industry – and not even allowed the comfort of sheep's clothing.

I refuse, however, to give the pharmaceutical industry the satisfaction of playing to the full the part allotted to me. It would be easy to do so; the adversarial scenario is not usually a difficult one to stage, and confrontation comes readily to many of us, even to women.

So I shall now leave the knockabout stuff and try and describe to you the preoccupations, the hopes and the fears of the consumer in relation to the drug industry. In doing so I shall to the best of my ability put myself in the shoes not of the reviled consumerist, but of the ordinary person who will be bound at some time in his life to be the recipient of pharmaceutical products.

To start with, the attitude of most of us towards them is ambivalent. We are ill, we want to get better, experience or knowledge or hearsay tells us that preparation 'X' will relieve our headache or reduce our fever, or whatever. We take it thankfully and take on a new lease of life. So far so good. But sometimes a prescription in itself becomes a talisman, and this unhappily is the case far too often when a patient does not get from his doctor the attention and concern which he seeks. The files of the Patients Association are full of cases of people who are unhappy with the attitudes of their doctor – the failure of communication. In this context – but widening it – I thought it rather sad that Dr Stuart Walker's triangle of essential communication lines between drug regulation interested parties had no slot for the consumer. He referred later to 'education' of the public in the problems and solutions of the drug industry – a point emphasised by Dr Wardell. What about educating the industry in the preoccupations of the patients?

Most of you will be aware of surveys which have been done from time to time about patients' attitudes to prescribing. They invariably show that the majority of patients expect to come away from the surgery clutching a prescription – original or repeat – and feel uneasy if they do not. And their GPs are too often only too ready to oblige. I say this, not because I am making a general condemnation of doctors' prescribing habits, but because I deplore it when it is used as a quick and easy way of concluding the consul-

tation. So, having got our prescription, half of us do not comply with the instructions, either because it seems to have done its work or because it has not, and leave it off mid-stream, putting the rest away in our medicine cupboard in case it should come in useful on another occasion. On the whole this does not happen because people think the preparations are unsafe, simply they have served their purpose (or in some cases may be discarded as useless).

People are, however, in general well-disposed towards their medicines, even if they are sometimes only surrogates for more human concern with their welfare on the part of their doctors. I doubt whether in this context patients concern themselves with the people, the firms, who manufacture the medicinal compounds. It was of course different in the old days when family doctors and the local chemist made up the prescription themselves. Now it is all impersonal and remote. (If only patients knew, incidentally, that – or so Professor Illich says – the typical general practitioner in treating the typical patient picks from an idiosyncratically assembled collection of no more than two dozen drugs, their fondness for prescriptions might wane.)

Impersonal and remote, that is, until some episode brings it home to people that things can go wrong with particular drugs and then the drug companies concerned can quickly become the villains of the piece. Alarm is generated which is in inverse ratio to the trust which patients had hitherto unthinkingly placed in the drugs they took.

Professor Teeling Smith – and Lord Vaizey took the same line – accuses 'consumerists' of wanting 100 per cent safety. Well, don't we all? But that is not to say that people do not recognise that there may be risks. But it is often very difficult for patients to extract from their doctors information about possible side-effects when he puts them on a drug which is new to them.

I put, therefore, top of my list of responsibilities to patients, the responsibility to ensure that they are given adequate information. I know of course that in the case of prescription only drugs, this is in the hands of doctors and not of the drug companies, and that the companies must impart the information to them (indeed it is of course available in data sheets) but one sometimes wonders how insistent company representatives are in imparting it to their medical customers.

I should like to see the use of patient package inserts developed in this country. I have seen examples of PPIs used in other countries which have a lot to commend them, including 8 word sentences.

I have suggested that we all want as individuals to be safe from risks – risks, that is, outside our own control. Commonsense tells us that that is not an achievable state, but while each one of you in the audience will recognise that the perfectly constructed motor car which never fails in any respect is a pipe-dream, none of you wants to be the one who draws the short straw and gets the car with the faulty brakes. I doubt whether you are all that philosophical about that prospect, so why should patients be expected to be so, when it comes to drugs over whose specifications and manufacture they have no control?

We, the consumers, in this situation expect two things of the drug industry – there are two responsibilities which we place on its shoulders: first, that the testing of compounds before they are marketed should err on

the side of over-caution – as many of you would, I suspect, see it. Secondly, that no patient is involved in a clinical trial without his consent – his informed consent, as the saying goes.

I know that there is a movement to moderate the severity of regulations in this country controlling drug trials. I have been reading a monograph prepared for the Office of Health Economics by Keith Hartley and Alan Maynard which argues that the cost of regulation in the UK to the community is anything between £30m and £85m, and that benefits do not measure up even to the lower of these figures. The authors ask, 'Is society willing to pay over £30m per year for any improved safety due to the 1968 Medicines Act?' and they go on, 'Also, it cannot be stressed too often that all drugs involve some risk. Regulation probably adds to the *mistaken* belief that drugs are perfectly safe and involve no risks. But then perhaps the legislation "protects" vote-sensitive politicians and administrators rather than patients!' (A remark in the context of the life and death issues we are discussing – and they are deadly serious – which strikes me as being in rather poor taste.)

The Patients Association is unashamedly hostile to relaxation, let alone abolition of the regulatory system. We believe that past and indeed present episodes where drugs have let us down, so to speak, do not encourage people to accept a less rigorous line. We tell the Department of Health: 'The safety of drugs has become of much greater public concern in recent years than it used to be. We believe that in the light of this the tendency should be to strengthen, not weaken, independent control over development of new products for the market. In particular we do not consider that export promotion should take precedence over this.' We do not argue for *longer* scrutiny, but for *impartial* scrutiny. Of course, we may be wrong to be so cautious, perhaps the good faith and dedication of the pharmaceutical companies would produce better results for patients, if there were fewer constraints on them. Certainly the Office of Health Economics believes this. I am not being cynical when I say that I have doubts. I do not believe that the medical teams in drug companies are unscrupulous people, far from it. But I do believe that commercial pressures may be such, in this as in any consumer goods industry where competition is strong, as to be a temptation to cut corners.

I was interested in Dr Hayes' remarks about freedom of information in the United States. In this country we are obsessed with secrecy – I had a recent example of this when I asked the DHSS for some straightforward information about the clinical trials etc, for Opren.

I said early in my talk that people are ambivalent in their attitude to pharmaceutical products. So I challenge the assertion in Professor Teeling Smith's background note that 'there is general consumerist hostility towards pharmaceutical innovation'. I suppose that if, collectively, we did require absolute safety for medicines, but believed it was unattainable, then we should condemn innovation on that ground. But since we do in practice recognise that there are risks, there is no logical bar to our welcoming innovation. And in general and in particular we do so. The ambivalence lies in, on the one hand, the reaction when things go wrong, eg, with whooping cough immunisation, and on the other hand the almost desperate pleas for a new preparation which is rumoured to have miraculous properties for

some intractable condition. Interferon has been a case in point recently when, so I have read, cancer sufferers have urged their doctors to prescribe it before its efficacy for that condition has been demonstrated. A sad story, and one that should be read as showing simply that consumers suffer from that universal characterisitic, the human condition.

I can understand the sense of injury of the pharmaceutical industry when they are attacked on both fronts – for providing us with medicines which in due course do some of us cruel damage, and for not providing us on the instant with effective remedies. The media are of course immensely powerful influences in this area. Through them we become familiar very rapidly with hitherto unknown substances, called, as it might be Halcion or Opren or Debendox, because there are reports of ill-effects on some people, often in other countries. Because people are interested in their health such reports attract wide attention, and may lead to panic reactions. They will certainly lead to what some of you may regard as an unwelcome spotlight once again being focused on the drug companies who will be accused of outrageous profits, exploitation of the Third World, to say nothing of beagles.

I am not going down that road, although I listened with much sympathetic attention to what Dr Sankaran had to say. But I do want to pursue a related point which harks back to the second responsibility towards consumers which I placed on the drug industry – the ethical conduct of clinical trials. This has been a subject of much public attention in this country recently because of the death of an elderly woman, Mrs Wigley, due, according to the inquest, to the administration of a new form of treatment which was being tried out on her without her knowledge, let alone consent, or that of her family. I condemn this absolutely.

I know the arguments used in such cases: the patient had cancer and the treatment was designed to reduce the incidence of secondary tumours. A reason given for not consulting the patient was that it was thought that it would be inhumane to reveal to her she had cancer. In fact it emerged subsequently that she already knew. However, if there were good reasons for not telling her, then she should have been left out of the trial. But then, horrors, it would no longer be a proper randomised controlled trial. Another reason often put forward for not asking patients' consent to participation in a clinical trial is that the whole business is too scientific and esoteric for the ordinary human being to grasp. Well, I daresay it is if doctors take no pains to moderate their language, or to translate from the Latin into English. But I do believe, and I know many clinicians who share this view, that informed consent can be genuinely sought by a straightforward explanation first, that a clinical trial is being arranged to help the progress of medicine in regard to a particular health problem; second, that there may be some side-effects of which some can be foreseen and may cause discomfort, but others may occur which have not been anticipated and if they are painful or disagreeable – and of course if they are harmful – the trial will stop; and finally, and this, I recognise, is the thorniest part, that the particular patient may or may not be given the trial drug. This last problem is illustrated once again by the trials now being sponsored by the Medical Research Council into whether the use of vitamin supplements could prevent spina bifida. I am glad to see that the MRC has said that no woman will

be entered in the study without her true consent, that is consent freely given with proper understanding of the nature and consequences of what is proposed, that is that one of the trial therapies is unlikely to have any effect on spina bifida.

Such explanations, some say, may ruin the validity of the trial, because the patient may imagine things. Better that in my book than to be exploited as research fodder without any choice in the matter.

A disturbing feature of the particular clinical trial which resulted in the death of the elderly patient, is that not only the ethical committee in her hospital, but also, it seems, ten other ethical committees, decided that the 250 people in the trial around the country were not to be informed of this fact. Ethical committees are supposed to include at any rate one lay person – although I believe not all do so – and the business of this member should be to stand in the patient's shoes, and in particular to remind his or her fellow members of the Helsinki Declaration, of which this country is a signatory. I am sure I do not need to quote it in full to this audience – as you know, the relevant section starts; 'In any research on human beings each potential subject must be adequately informed . . .'

The Patients Association considers that the Department of Health should play a more positive role in monitoring the composition and work of ethical committees, than it has done hitherto – at least so far as the naked eye can detect.

Finally, suppose something does go wrong as the result of the administration of a drug, in the course of ordinary treatment. Where does the responsibility of the manufacturer lie? At present, the position in the UK is unclear, other than that it is not in favour of the patient who has been the victim. The unanimous view of the dreaded consumerists in this country is that the manufacturers should be subject to strict liability and, moreover, that that should cover development – the state of the art, as it is rather oddly called – as well as manufacturing. However, having said that, I do not, any more than you do, I expect, although perhaps for different reasons, regard it as the ideal solution. The position of the prescribing doctor as the intermediary would present formidable legal problems, as also would the compulsion which understandably the drug companies would, I presume, feel to ensure that the patient is informed of every conceivable side effect and contra-indication, no doubt to his complete confusion.

The preferable solution would, in the view of my Association, be a no-fault compensation scheme. Of course that would not solve all the problems, since the causal link between the drug and the medical injury would still have to be established, but it would go a lot of the way to remove the hassle and the bitterness which now is usually a feature of unhappy experiences of victims of drug mishaps. And unhappy for the drug companies too, because I do believe that they recognise responsibilities to the consumer, but, may I suggest, they see them in global terms, whereas I see them in terms of Mrs Wigley. Indeed, after listening to a number of the talks at this symposium, I found myself adding two more roles to my brief: the toad beneath the harrow and the worm's eye.

An industrial view

Dr Dick Joyce
Ciba-Geigy AG, Switzerland

To give the industry view that the programme requires, I am less qualified than the monkey in the Basel Zoo who, you may remember, after being taught to distinguish accurately between photographs of humans and those of apes, was given a mirror together with a photograph of himself. With only a moment's hesitation, he put his photograph with the pile of photographs of human beings. In such circumstances, I would have been less confident. As it is, I would like to assume that the programme title 'An industrial view', is a misprint for 'an individual view'. I also misread pharmacological as pharmaceutical in the title, but that may confer some benefit.

The opinons that follow, therefore, are strictly personal. There can in any case scarcely be an official view of matters that are themselves so heterogeneous. The possible consequences of the second pharmaceutical revolution are not likely to occur uniformly throughout the world. Not only are there from three to six worlds, depending upon your arithmetic, but the problems of even a single country within one of those worlds are not the problems of another.

The impossibility of prediction

The speakers in the final session have been asked to predict relationships between the industry and the society of which it is a part. But only one thing can be predicted about the future. The future will be full of surprises, like a Russian official history.

However, even surprises, if they occur often enough, can create a pattern from which rules may be extracted. For example, it seems that the widespread introduction of almost any kind of high technology is frequently followed by a profound change in sexual mores. This has been the case for the stationary steam engine, the automobile, the cine-camera, some well-known products of the first pharmacological revolution and now, it appears, the adoption of citizen's band radio as well.[1] But high technology usually has limited relevance to 80 per cent of the world's population.

One of many reasons for the inaccuracy of prediction is that, for better or worse, the prediction may affect the outcome. Fewer disillusioned voters may wish to elect a member of the opposition if they realise in time that so many others intend to do likewise; predictions of recession may either reduce confidence in a failing economy still futher, and so accelerate the recession, or they may promote counter-actions that are, for once, successful in delaying it. It is always easier to build models of the past than of the future. The past has happened by the time the model is constructed, and it is only in science fiction and societies like that of '1984' that the model can change the *past* events that it describes.

However, science describes in order to predict, whereas management predicts in order to influence; the main purpose of prediction by industrial

management *is* to influence. (This is one reason why 'management science' is a contradiction in terms.) It predicts the state of the relevant market in order to be able at least to maintain or perhaps enlarge its market share. With the oldest of management skills, innovation or entrepreneurship, a new market is identified; it may not even at the moment exist, but arise from the creation of a need not previously felt to exist at all. Market creation is undoubtedly still a management activity in some industries (video-games, perhaps, or a liqueur based on water-melons), but it has not been a typical activity for management in the pharmaceutical industry, and will not become one during the second revolution. The need for health is always consciously perceived by the consumer of means to its attainment, though not necessarily the means by which it is provided. The prediction that a market will cease to exist is also not unknown, so that it will in fact collapse and the predictor, full of *Schadenfreude* on the sidelines, fills the gap that he has helped to create. Some have already predicted the multinational drug industry as a whole into non-existence. Perhaps such people are seeking the honour of a self-fulfilling prophet, especially in another's country.

Decline and restoration of confidence

An industrial view of the sociological consequences of the Second Pharmacological Revolution and a sociological view of its industrial consequences are not necessarily very different. For, to paraphrase de Maistre, each society gets the industry it deserves, just as industry helps to create the society of which it is a part. Each of us is a producer as well as a consumer, of primary or secondary goods or services. If a sufficient number of us, as consumers, do not object to what we are doing as producers – whether of Muzak in elevators and supermarkets, the video of violence, or tobacco smoke everywhere – there will be too little control of problems because they have not even been defined as problems. This may be the case with the pharmaceutical industry at present. Although its ethical products are directly advertised only to a small subsection of the population, the products as well as those to whom they are advertised have played a larger and progressively less avoidable part in the lives of all of us, at least in the developed, or over-developed world. It is common for that which is inescapable to be praised: the profession and the pharmaceutical industry were in relatively good standing, in spite of criticisms from the time of Aristophanes onwards, until the 1950s.

Burnham[2] has defined four main reasons for the decline in prestige of the medical profession in the USA since then: the relatively sudden emergence of chronic instead of acute illness as the main focus of medical care; the growth of large medical institutions and their attendant bureaucracies; the increasing sophistication of consumers; and the rise of psychological explanations for illness – patient and practitioner were not prepared for confrontation with the growth of the medical model for social problems and the consequent explosion of psychosomatic illnesses.

To these factors, especially the first and last (which have without doubt also affected public attitudes to drugs), may be added two others, the first of which, perhaps, affected industry alone.

First, the tremendous successes of antibiotic therapy created understandable but incorrect assumptions that the drug treatment of non-infectious diseases would be no less effective. However, some lay inhabitants of developed countries, at least, have begun to limit their expectations of drugs and organised medicine to lesser goals than the solution of all personal and social problems, the prolongation of life at high quality and the heightening of abilities and experiences without regrettable consequences. But they probably retain the same expectations of other life patterns and unorthodox kinds of therapy.

Second, the scientific quest for understanding, for precision, has led to profound changes in the relationship between society and the individual. Increasing precision in astronomy, for example, moved mankind from the centre of the universe to the periphery of the solar system before bringing it face to face with God without intermediation; precision in the life sciences erased the boundary between man and other living forms; the behavioural sciences blurred the frontiers between instinct and conscience, intellect and intuition within the individual. Without attaining very much precision at all, the political sciences have virtually abolished the concept of the individual altogether. Indeed, all the fashionable models, religious, scientific and political, are increasingly threatened by the statistical. Of course there are still priests, psychiatrists and prime ministers. But a dominant discipline in medicine now, as in economics and sub-atomic physics, is the calculus of probability. Individual certainty, or the search for it, has been replaced by measures of central tendency and dispersion, of group conformity with the norm; by the substitution of the laws of chance for statements that used to be definite, even if they were incorrect. They may provide a better model of the universe and thus better medicine and better drugs, but they are not necessarily perceived by the individual as helping to understand his or her needs and actions.

This is not a digression. The present growing points in clinical medicine are concerned with prevention, with community health and with its associated epidemiology; the major method of clinical pharmaceutical research is the controlled trial; the existing developments in basic research depend upon the use of bacteria. All these trends are concerned with groups, not individuals. To take a recent example. A paper in the *British Medical Journal*[3] on the treatment of myocardial infarction comments that 'while an improvement in mortality of 25 per cent may sound impressive, in reality it represents a change in death rate from 8 patients per 100 to 6 per 100.' But for each of two so far unidentifiable patients, the death rate has changed by 100 per cent.

Whatever the reasons, public trust in drugs, as in the practice of medicine itself, is thus considerably less in 1982 than it was in 1500, or even in 1950. The means of restoring that faded trust are to be sought at least in part by reversing the trends that have caused its loss. This need is the first consequence of the new revolution. Other kinds of impact on the industry itself should also not be forgotten. They are not necessarily identical with those on society at large.

What is to happen in the developing world, with its 3 billion inhabitants, should also be considered, independently from the changes that will affect the 25 per cent minority of us, although it is we who consume 81 per cent

(1978) of the world's entire pharmaceutical production.[4] Sir Douglas Black and Professor Zaki Hassan have reminded us in different contexts that a major function of a nationalised industry, whether it is the British National Health Service or Pakistani pharmaceuticals, is to be fair to its employees as well as (or possibly even rather than) to take efficient care of those who consume its services.

Possible changes in the developing countries

The smallest group to be considered is that of industry in the developing countries. Methods of production continually become cheaper and simpler, and the pressure on selling prices greater. Developed industry can be expected to make increasing room for the developing world to produce established products and the latter world will clearly benefit from such changes. In consequence, major industry is already exposing more of its inner machinery to public examination – not only the methods it uses to determine the efficacy and ensure the safety of its products, but also its methods of decision-making, especially about prices and profits. Its exposures will have to be exercises in truth-telling, not in public relations, and they will be the better for making this distinction. In the long run, trust will be recovered by the discovery and exploitation, in the best sense, of new products that deliver the promised benefits that were earlier implied; especially if this is achieved without making unfulfillable promises. As this symposium has richly shown, such products are in the pipe-line already, and if promises about them are made and not fulfilled, the new disappointment will not be forgiven.

Apart from the creation of more jobs in the developing world by the transfer of technology, an even more significant benefit will be the greater number of patients treated with drugs that were previously unavailable locally. On the other hand, many drugs irrelevant to major local health needs may become harder to obtain;[5] life for many members of the wealthier classes, especially in large towns, may thus become more hazardous, though the great majority of people are unlikely to be adversely affected. Regulatory skills will not spontaneously improve in proportion; because other relevant aspects of local tradition will not necessarily change either, quality control and distribution are unlikely to keep pace with the revolution. Dunhill[6] is cautious about the benefits of technology transfer for this reason. He considers that local production is likely to be urban, whereas most consumption is rural; distribution will therefore remain a critical problem.

There will be others. The reporting of adverse reactions by physicians from the developed world, as well as their interpretation, even now leaves much to be desired; that by their colleagues in the developing world is even less likely to improve as more drugs become more widely available. To take one aspect: Inman[7] has pointed out that generics complicate the attribution of causality in unwanted reactions by making it difficult to identify the source of the material responsible. This is especially likely if the event had seldom been associated previously with the drug under question. It is not satisfactory to argue that events previously unrecorded in the developed world will not occur elsewhere; or that, if they do, they will be unimportant

or infrequent. It is certain that some aspects of drug response are culturally determined; there are genetic and biochemical differences, too, and monitoring is needed and must be maintained. On the more positive side, Buckles[8] suggests that because western (or northern) products cannot always be adapted for southern use, and because it is often very hard to adapt important features of the local environment (sanitation, transport and so on) that interfere with the best use of drugs developed elsewhere, specific products must be developed that are suitable for local use. This need not be expensive or time-consuming: more appropriate packaging, in regard to both quantities and ease of distribution, could do much. Buckles' own examples include injectable or implantable contraceptives that are acceptable to some simple communities although they may be rejected by sophisticated altruists; ocular delivery systems for the already damaged eyes of patients with trachoma; and, in general, treatment for diseases such as onchocerciasis and trypanosomiasis that he describes as 'suffered by people who can never afford to pay for the treatment.' Of course, some products from the first world may simply have been directed to the wrong targets. Dobbing[9] proposes that the mother should take prepared milk and not her baby. The demographic consequences will be hard to predict, since they will affect both of them: more babies will survive, but intervals between conceptions will probably be prolonged. It may be that there will be less political objection to this than to the use of Depo-Provera or self-administered prostaglandin suppositories.

A start has been made in the right direction by the collaboration between WHO and IFPMA[10,11] in the provision to selected developing countries of 135 drugs in the WHO Essential list. Over 230 offers have been made, by a total of 46 companies in 11 countries, including 5 Swiss and 2 British. They should be cheap, of high quality and adapted in their formulation, presentation and packaging to the contexts and climates of the countries in which they will be used rather than of those in which they were developed. Other speakers at the IFPMA meeting at which this news was announced were less sanguine about the end-results. Wood,[10] for example, described the situation in parts of rural Kenya in terms of some ways also appropriate to medical practice in many parts of Europe (2 minutes for each patient, 50 per cent incorrect diagnoses and/or prescriptions and massive inadequacies in patient compliance); but all these problems were encountered with medical auxiliaries, not medical practitioners, and on top of them were piled a more than 50 per cent loss of drug supplies due to breakage and leakage, and major difficulties with the quality if the supplies were received at all. Lall,[12] an economist who had previously been vehemently opposed to an independently supplied drug market, described his government's attempt to control the Indian drug market as a disaster. In fact, the relatively high proportion contributed by the cost of drugs to the health bill of developing countries is often represented as an extravagance rather than an economical way of lowering the incidence of diseases in the absence of feasible alternatives. The limited resources of poor countries (as of the less poor) should be used as efficiently as possible. They may frequently need to be applied to targets outside the manifest health system, such as irrigation and education, in order to achieve more than money spent directly on primary health care itself.

Some possible changes in the developed world

What will be the effects of the revolution on the practices of northern, or western, industry? The pure, 'natural' products should eventually have toxicities that are little different in quality and degree from those that the metabolism of the human body itself generates. Their therapeutic effects, too, should be better localised to the appropriate site of action either by their intrinsic properties or those of the new delivery systems designed for the purpose.[13] These factors – specificity of action, freedom from toxicity, especially of an unexpected kind, and above all the naturalness of the products – will help to restore confidence in the industry. 'Probably no other products are as affected by social, political, ethical and commercial pressures as drugs', writes Dunhill.[6] These pressures, many of which are generated in the developed world for reasons that are not always concerned solely with improvement in the standards of health care, should be modified by the perception that the major drug companies are no longer directly producing drugs of the traditional kind. Of the world's widely spoken languages, it seems that only in English has the word 'drug' always borne the double connotation that was formerly divided in most others: 'drogas', 'Drogen' and 'drogues' are almost exclusively used as general terms for junk, stuff and other less polite words for illegal substances, a special word – such as médicaments, Arzneimittel, *φὰρμακα* – is usually reserved for the tools of the medical trade. 'Medicine' and 'medication' of course exist in English but the words are not used so much nor in quite the same way. In current usage the two concepts have now come to overlap in most languages.

Although the legitimate industry's reputation has therefore been tainted by linguistic association with the illegitimate, the association is not only linguistic but historical as well. Almost all powerful centrally active substances used for non-medical reasons in the west – morphine, heroin, LSD, cocaine, amphetamine, 'Ludes and Angel Dust; in fact, all except the organic solvents and cannabis and its derivatives – were first introduced as medical remedies.

Industry in the developed countries will welcome its impending divorce from 'drugs', no matter what the language in which the decree is handed down; but account will also have to be taken of other negative public attitudes that affect industry, and society as a whole. These include the still-growing 'anti-science' movement; and the feeling that it is immoral to make a profit from trading in matters of life and death. The first is surprisingly widespread; it censors Texas school tests for references to insulin as a beneficial drug,[14] it is even manifested in the tendency of the managements of some presumably scientifically-oriented organisations to rely upon such unproved, unprovable, disproved or discredited techniques for help in decision-making as graphology and astrology. The obvious questions must be asked: how likely is it that an unscientific world, or an anti-scientific one, would be even a tenth as liveable as the present one? Is it less moral to make smaller profits from trading in life and infrequent accidental death than those from trading in certain death alone? The best defence against both these negative public attitudes will be the success of the second pharmaceutical revolution itself.

Speculations

Broadly speaking, possible new products fall into one of two main classes. The first class consists, in the main, of hormones, antibiotics and certain diagnostic preparations. The second class consists of totally new developments: the substances that offer the possibility of counter-attacking as yet intractable diseases, of diagnosing and treating the prodromal viral stage of certain carcinomas, of correcting genetic errors at the cellular level. Some will become realities but not all of them will be welcome to everyone. There is certain to be opposition as well as enthusiasm for the development of a treatment for genital herpes; if successful, this could relaunch the apparently flagging sexual revolution and make the need for an effective combined contraceptive and anti-venereal even more imperative. But, more generally, the power conferred by being able to make, in quantity, any molecule that exerts a control function of any kind will be seen by some less thoughtful people as hastening in the rule of Big Brother. Chemical control might replace conditioning; the well-behaved model of future society could be that predicted by Stanislaw Lem rather than that of George Orwell. Sandler's claim[15] to have isolated 'Tribulin', a naturally occuring anxiety molecule that competes with benzodiazepines, may be a precursor. Such developments can always be used well or badly. In themselves, they do not change the major objective of mankind – as individual, family, community, market and world – to seek a balance between control and accommodation. They could even present a greatly improved opportunity to reach those ends by reducing conflicts, improving learning and the quality of decision-making upon which their attainment depends.

The consequences of improved methods of diagnosis are likely to differ between north and south. In the south, the emphasis will be epidemiological – diagnostic screening of whole communities for filariasis or schistosomasis will lead to better estimates of prevalence and so to more awareness of the magnitude of the public health task; whereas in the north it is the individual who will benefit from more appropriate treatment.

Because the chemical and biological advantages of the new substances will have to be proved, there will still be a need for clinical trials and toxicity testing. There will be considerable methodological advances in both. Greater precision in the definition of indications, the consequent omission of irrelevant controls, the accelerated communication of results by the use of intelligent hardware in laboratory, office and clinic,[16] will all help to restore the numbers required for trials to more manageable proportions. Large reductions in sample size may even be achieved from the return of differences between treatments that can be seen without the aid of a statistical magnifying-glass at all. New kinds of evaluation are also to be expected. A promising line is the use of more appropriate analyses of cost, or risk, and benefit tradeoffs as a measure of outcome: change in the individual's own perception of the quality of his life is a complement to and may even be a more appropriate indicator than impersonal estimates of that life in dollars or roubles. The kinds of observations often wrongly distinguished as 'hard' and 'soft', biochemical and behavioural, may combine with spectacular consequences for the quality of life and even affect its duration. Long-term storage of biological samples to test subsequently formed hypotheses by delayed analysis is already paying dividends, as Beasley and his collea-

gues have shown[17] in their study of the relationship between hepatitis and hepatic carcinoma. If the exploratory techniques of Lissy Jarvik and her collaborators at UCLA[18] for determining individual 'distance from death' can be translated into practical applications, fine-tuning the later part of individual lives will become a reality.

If no more, experiments of these kinds may have a profound influence on experimental epidemiology. Time consuming, expensive and frequently equivocal retrospective studies may become as unnecessary as often irrelevant or sometimes poorly designed and almost always misunderstood toxicity testing.

Conclusion

The organisers did not invite the participants to consider the effects of the fourth or fifth chemical revolution[19] or the so far endless industrial revolution as a whole. The pharmacological revolution is only a part of that context, within which predictions of the sociological consequences even of the pharmaceutical revolution become even less reliable. For example, will the recent failure of an OAU summit to reach a quorum[20] modify the political and pharmaceutical future of the African continent? In the other world, how will the changing demography of the USA – 2 employed for every 1 retired in AD 2000 instead of the 4:1 today[21] – alter the needs and systems of health care delivery? To take a more specific example, Flewett[22] asks if a vaccine is likely to be effective for controlling virus diarrhoea in children. He answers: 'We can only hope so. (But) even if it is, the job of saving the children will only have begun; births will have to be controlled and food provided. Viruses and malnutrition are synergistic causes of death' – as, one may add, are poor education and other grounds for failure to use technical skills to the full. Levy and Sondik[23] have emphasised the need to evaluate new knowledge as fast as possible, not least in order to decide on the wisest allocation of limited resources. Once validated, new knowledge should also be disseminated and used as fast as possible.

Although Klarman[24] firmly believes that technology monitoring is a better basis for planning than is forecasting, I risk a final pair of random but safe shots at the moving targets of the future. It will be a mistake to follow blindly in our present directions – further development of the already over-developed, the continuing replacement of thought by things. We shall do better to define and meet the real needs of our majority partners in humanity as well as of ourselves.

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Discussants

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May I first thank the speakers for excellent presentations and for opening up for discussion the social implications of the Second Pharmacological Revolution. It has been made abundantly clear that there is considerable scope for further therapeutic advance as a consequence of our increased understanding of body and other systems. However, as has rightly been said, it would seem inevitable that such progress will continue to generate areas of conflict between the industry and the consumer groups. Yet, at the same time, these two groups share areas of common interest and there is a role for partnership. The pharmaceutical industry would be well advised not to ignore the consumer organisations and at the same time to judge as objectively as possible the criticisms that are levelled against it.

Accepting Dame Elizabeth Ackroyd's approach as representative of the consumer's view, I do not believe that many of us would disagree with her basic statements. I would venture to suggest, however, that there are other groups which have much more extreme views and which obviously desire confrontation. I refer, for example, to one of the groups mentioned by Dame Elizabeth – Health Action International. You may recall that in their opening press statement in 1981 the following remarks appeared: 'We agree unanimously that the multinational drug industry is deeply implicated in trade in hazardous, useless, inappropriate and often unconscionably expensive drugs, and we are unanimously agreed that we will not tolerate this ill-treatment of consumers, particularly when they are sick and poor.' It went on: 'When the sharks work out a code on how to treat the fish, it is time for the fish to get together and decide how they want to be treated.'

An international trade union organisation recently held a conference in Moscow with a specific remit to take action against the pharmaceutical transnational corporations for a health policy in the service of mankind.

The International Federation of Chemical, Energy and General Workers Unions has indicated that it has a hit-list of pharmaceutical companies, and sees itself as one of the few bodies that act internationally to bring the multinational pharmaceutical industry under responsible social control.

These are only a few examples of what I believe is a quite destructive attitude and not conducive to reasonable debate and resolution. Unfortunately, that sort of extremism is much more exciting to the media than the vast amount of constructive discussion that goes on. Of course, one of the problems is that balanced discussion and education do not sell space or newspapers.

I should like to quote another example, this time from the *Financial Times* of 15 September. This is a rather small affair, without banner headlines, but it is important. The President of the Pharmaceutical Society, at its recent annual conference, made the following observation: 'All the brews of the witches of *Macbeth* are now thought to be preferable to the safety, quality and efficacy of modern medicines. Apprehension over modern medicines was being caused by the sort of publicity given to the withdrawal of product

licences for medicines thought to produce serious side effects. The Medicines Act of 1968 was introduced to control the safety, quality and efficacy of medicines. All medicines have side effects if they are pharmaceutically active.'

I think that everybody recognises that. The problem, as we and many other people have said, is that we have to equate the risk to the benefit.

Constructive discussion between the pharmaceutical industry and many governmental and other international organisations – for example, the WHO – to find ways of solving some of the problems of health care, has been going on for a long time. Dr Sankaran knows, as I do, that the recent initiative mentioned by Dr Mahler at the World Health Assembly this year took three or four years to develop: from creating an understanding of common ground to the construction of plans for action. The action that we propose to take will begin in a small way with pilot schemes, but at least that is preferable to some of the other things that have been and are being suggested.

As an aside, it is rather interesting to note that at the recent World Health Assembly the view was accepted that WHO needs to protect its intellectual and industrial property and the decision was taken to patent the results of any research carried out by the organisation itself or by others on its behalf, so that at least we are talking the same sort of language and facing similar sorts of problems.

As Dr Hubbard mentioned in his presentation, health involves many factors. He talked about nutrition, hygiene, sanitation, clean water, decent housing, among others. The contribution of the industry is only one factor and one relatively small part in the solution. Much play is made that the international industry, if I may use a colloquial expression, 'rips off' the poorer countries. Yet when companies make available to poor countries products at significantly lower prices than for developed countries, it is not uncommon for entrepreneurs to re-import the same product from a low-price country back to its country of origin for re-sale at either a marginally or a significantly lower price, claiming that the original company is making excessive profit and frequently implying that not only is the industry ripping off poor countries but rich ones as well! What is frequently not understood is that the now fashionable so-called 'parallel importer' is making much higher profits than anybody else.

If we are to assess the possible success of the Second Pharmacological Revolution – if it is going to take place and to be allowed to benefit the health of mankind – we also have to face the real world. Those who risk the research, investment in resources, finance, time, clinical studies, registration, and so on, have to be able to recover the cost of that research and to make reasonable profits to refinance further work, otherwise it is obvious that the skills of the scientists will either be wasted or they will not, frankly, be available to make the revolution happen.

Equally important is the dialogue between industry, government and international agencies to ensure the efficient use of resources in the pursuit of realistic and achievable goals. It is also essential to recognise that the term 'social implications' means quite different things in, for example, the Western world, the industrially developed countries, the developing nations and the less developed countries, so that an appropriate scenario reconciling health care priorities, funds available and other factors has to

be constructed for each environment. Unless we can face the impending Second Pharmacological Revolution in those terms, in the real world it will not happen.

This industry is on record in many places – I shall not develop the theme here as I have in many places before – as being a responsible industry. As far as I am aware, we shall meet our part of this revolution in the interests of the world's health care.

MICHAEL PERETZ

International Federation of Pharmaceutical Manufacturers Associations

The social implications of pharmacological advance constitute an important subject and I am very glad that it has been put on the agenda for this meeting. If we cannot get the social scene right, there will not be a new pharmacological revolution. If the social climate is not favourably disposed to the sorts of things that the industry can achieve, not only will the industry suffer but so too will the world's population at large.

I suppose that I have been invited to be a participant in this discussion because of my experience as Executive Vice President of IFPMA over the last four years, where I have been the target for a good deal of comment and criticism from activists in the anti-pharmaceutical industry lobby.

Experience has demonstrated to me that there are three ways in which the pharmaceutical industry can react to such criticisms. The first is to ignore them. I believe that the industry will do that at its peril, but it remains a very easy trap to fall into. Many of us – myself included – have been involved in problems with the media. What we have said has often been selectively reported. It has been an eye-opener to me to find that television programmes can be 'edited' in such a way that one's original statements become completely distorted. I know that many leaders of industry feel that getting into that sort of dialogue with the media is so non-productive and can create such problems that they would rather not get involved at all. My advice is, however, that no matter what the hazards, do not ignore them; persevere and make your case as best as you can.

The second reaction is for the industry to become side-tracked into discussing the critics' qualifications and motives. This too is a very easy trap to fall into, not least because much of what the critics have to say is often poorly researched and coloured by half-truths and selective reporting. Such criticisms may seem particularly hard to bear for an industry which has to satisfy so many regulatory and government authorities as well as its important responsibilities to its own shareholders.

I believe that the correct reaction is to address ourselves to any matters of serious consequence raised by the critics, and either to endeavour to explain their misapprehensions or to consider whether changes should be made. I believe it is the only way and that the industry should beware of endeavouring to defend the indefensible. Sorting out the wheat from the chaff is by far the most difficult way of meeting such criticism, and the industry should beware of getting side tracked, in the way that I mentioned, into discussing the critics' qualifications and motives.

Much of what Dame Elizabeth Ackroyd has said in her presentation is incontrovertible, and I can assure her that the industry sees no advantage in

adopting a confrontational attitude towards representatives of consumers such as herself; indeed, the international industry has been at great pains to endeavour to enter into a dialogue with our critics, only to be faced all too often with the response, 'My mind is made up – please do not confuse me with facts'. I say that with feeling as I have had recent experience of this attitude at a WHO meeting in Bangladesh.

There are, however, one or two points in Dame Elizabeth's presentation on which I should like to comment. I would hardly rely on Professor Illich as a reliable source of information on what a typical general practitioner would prescribe. The suggestion that there is no control over the specifications and the manufacture of drugs creates the impression that Dame Elizabeth has never heard of the army of Government inspectors who visit pharmaceutical factories, nor of the laborious and time consuming provisions of the Medicines Act under which the specifications for pharmaceutical products are closely defined and monitored.

However, it was the mention of whooping cough immunisation in the latter part of Dame Elizabeth's talk that particularly aroused my attention. The facts as set out recently by the Government are that the health risks to children in being vaccinated against whooping cough are one in 100,000, while the risk of contracting the disease among unvaccinated children is at least one in 30, and the risk of a child dying from whooping cough itself is one in 3,000.

We have been reading in the newspapers this week and last week that the number of cases of whooping cough notified to the authorities in England and Wales, is currently running at over 3,000 a week. In the papers this morning, it was reported that another child has died of whooping cough – the fifth in England and Wales. This enormous rise in the incidence of whooping cough undoubtedly owes much to the fears about the safety of the vaccine expressed publicly – no doubt for the best reasons – by individuals who must now bear at least some of the responsibility for these disturbing developments.

I should like now to say something about pharmaceutical problems in the Third World. I have just returned from Bangladesh and my visit there has helped me to focus clearly on the important issues that have yet to be resolved.

One of the difficulties is reconciling the Third World's anxiety to industrialise with its demand for cheaper drugs. Although there are bound to be exceptions, on the whole it is likely that drugs made in newly built small factories set up in the Third World are likely to cost more than drugs that are manufactured in large-scale plants in the Western World that were built many years ago and have therefore been depreciated to a fraction of their original cost. To suggest that major savings in foreign currency would flow from increased manufacturing capacity in those Third World countries is a disservice to the people there. If much of the plant to set up these factories has to be imported, there may not be any saving in foreign currency at all; indeed the reverse may be true.

The international industry is all too often used as a convenient whipping boy. If it sells its drugs at a low price to the Third World, it is providing uncomfortable competition for local industries. If it sets up local factories, as it did in Bangladesh, to manufacture the products that the local private sector

is prepared to buy, the Government may turn round and say, 'We do not like you selling these products. You must stop selling them and start making something else.' It is often sadly true in many Third World countries that there is virtually no public sector market for drugs, and that leaves the industry in a dilemma. If the industry offers to transfer its technology to a local company, it is told that it should do it for nothing or for some quite derisory sum of money, despite the fact that the technology has cost the company a good deal of money to develop.

It is my belief that the problem in most cases is to persuade governments in the Third World to give a higher political priority to the health sector. Incidentally, on the subject of Bangladesh, I should like to emphasise that the industry has no argument with that country's government's desire to have an essential drug list; that is its prerogative. What it can do and has done is to point out that there is perhaps some possibility that the government may have 'thrown out the baby with the bath water', and that some of the drugs that are to be banned are not so bad after all – and that banning alone cannot do much for the health of the people of Bangladesh. But of course the Bangladeshi Government has the responsibility of deciding what to do as far as its own legislation is concerned.

What the industry can do – and what I am glad to tell you it is doing – is to try to build some sort of bridge with the WHO and with some of the governments in the poorer countries, to find ways of supplying drugs to people who need them at the lowest possible price. That is the most hopeful sign for the future.

I agree entirely with what Professor Joyce has said about the need for more truth telling. We might make a start as an industry by explaining what the industry means by the word 'profits', or, as is so often said, 'outrageous profits', whatever they might be. These profits have to pay for the approximate US$7 billion research that is carried out by the international pharmaceutical industry. Incidentally, the United States industry alone spent US$2.5 billion on research and development in 1981.

In the constant battle that is going on with governments and industry critics for lower prices, the need for financing continuing research seems to have been forgotten. One absolute certainty is that we shall not have a 'Second Pharmacological Revolution' unless at least this scale of expenditure continues.

PROFESSOR COLIN DOLLERY
Royal Postgraduate Medical School

As good a point of departure for my discussion as any is the brief interchange concerning Ivan Illich, who wrote extensively about the medicalisation of life. We are discussing social implications, but most speakers have considered them in a medical framework that puts a very high priority upon survival and health, perhaps to the exclusion of some other things. It is assumed that society has a very high expectation of survival and that health is possible only in societies which are relatively prosperous and free. If there is war, the means we adopt now for the very long-term treatment of diseases with a relatively good life expectancy would quite likely be abandoned. In severe poverty, in unemployment and in loss of liberty – that is, when people go to

prison – such priorities tend to change very radically. We should not assume that the world will become progressively more prosperous although, with the rest of you, I hope that it will do so. If it does not, much of our discussion may turn out to be irrelevant.

Making the assumption that the world will continue with a sufficient degree of prosperity to have this very high degree of expectation about health, what will be the role of drugs in that future? I think it is a large one but then I am a pharmacologist. However, I do not think that it is the only or necessarily the most important one. In response to some of the things that I have heard in this meeting – not all of them in the official papers – I should like to say that I think that the supply of drugs by itself, without the support of skilled personnel is of relatively little value. Consequently, some of the efforts that are currently being made in relation to the Third World to supply drugs at low prices, or perhaps free, to countries with very little in the way of an organised medical care system, are in my view misdirected. I do not think that drugs – except for a very few over-the-counter medicines – are of much use unless employed with a reasonable degree of skill in diagnosis and management.

As an example, we have only to look at some South American countries, where antibiotics can be bought over the counter by anyone with the money to purchase them. The results are certainly not very gratifying in terms of the control of infectious disease.

If drugs are to have a major role it is helpful to consider in what aspects they will have such a role. Inevitably discussions of this kind tend to focus on life and death issues such as the cure of cancer and of fatal tropical diseases. That is a very important role, and in the first pharmacological revolution the control of infectious diseases was one of the major successes. But one should not forget the relief of suffering and even the positive promotion of wellbeing as important objectives of pharmacology and therapeutics.

To take one or two examples at random: backache, insomnia, and grief are not diseases which commonly lead to people's deaths (although they may occasionally do so) but they are important targets of drug therapy and will become more important in the future if we are right in supposing that people's expectations, not only of survival but of reasonably pleasant survival, are to be fulfilled. These objectives may also become more significant as the number of people increases.

I now want to consider what the role of the pharmaceutical industry – of which I am not a member – will be. Although I think it is a very important industry, I perhaps do not have quite such a high opinion of it in all respects as some of those who work in it and manage it. Over the last few years, although the industry has tended to portray itself – and often to believe itself – as energetic and highly original, it has not usually been the originator of the scientific discoveries that led to the production of important new drugs; nor, do I think that it will be in the future.

Some of the large companies, including some of those for which I have the highest regard in terms of their research achievements, could properly be described as cautious, bureaucratic, and occasionally even as slothful in their progress. It is paradoxical sometimes to find industrial managers being extremely critical of regulators in government, for in some of those same companies the fabric of committees is such that it takes them almost

as long as the Food and Drug Administration in the United States to deliver a decision!

But although I may be critical of the pharmaceutical industry, I am quite clear that it is necessary. If it did not exist one would have to go out and create it. If society needs new drugs, as it does, it necessarily must have the kinds of expertise in medicinal chemistry, toxicology, and the clinical study of drugs which exists within the pharmaceutical industry. In some important areas of science, such as medicinal chemistry and toxicology the industry has by far the greatest concentration of skill. So the pharmaceutical industry is a necessary mechanism.

If the drugs and the industry are both necessary, where do the major problems lie? There is obviously a major problem in the field of innovation. The more we know, the more difficult it is to surpass what we already have and the time scale of originality has been lengthening over the last 10 years. If the number of major drug discoveries made between about 1945 and 1955, are compared with the number of major discoveries made between 1965 and 1975, we have to conclude that there were fewer of them in the later period, although there were several extremely important ones.

There will be a problem over innovation in the future. I sometimes wish that I could hear the pharmaceutical industry speaking up more loudly in this country and in some others where governments are cutting back on expenditure in universities, because it is not in their long-term interests that this should be happening. If universities are to perform their proper function, they will be the main place where new knowledge originates, and the pharmaceutical industry necessarily feeds on that new knowledge in the biological sciences and chemistry. Particularly when we have governments in many countries which are not altogether well disposed towards universities, those of you who are influential and know where the truth lies could be most useful to us in our times of trouble.

Another problem which is very real and difficult is the convergence of benefit and risk. It can be clearly seen in my own sphere of interest – high blood pressure – where we have progressively lowered the severity of hypertension at which treatment is commenced. The most recent trial in Australia showed therapy for mild hypertension generated a reduction of mortality of about two lives per thousand patient years of treatment. Most of us would probably think that worthwhile; it is obviously so for the two whose lives are saved. But if we work out the cost we see that it is becoming very high. There must come a point in time when either society decides that the cost is too high or society becomes concerned about the reasonably well-established short-term risks. Clearly, the amount of largely unquantified long-term risk that is acceptable must be less if the benefit is less. In a number of diseases we are beginning to be confronted by this issue.

Another area of concern touched on by several speakers has been the adversarial relationship that seems to spring up when things go wrong with drug therapy. Compensation for drug-induced injury at present depends upon establishing blame, by which I mean negligence. Some of those like my colleague, Desmond Laurence, who are much concerned by the issue, have suggested that one should no longer have to establish blame; all one should need to establish is cause. That would be expensive but it would be possible, although very difficult in some cases. It still seems to me to be

inherently illogical. I am not entirely clear why someone who has been damaged by a drug that has been given to him for good reason and to bring benefit should receive a large sum of money when the relatives of somebody who has died as a result of a complication of surgery, let us say in a gall bladder operation that was properly indicated but had an unforeseeable adverse outcome, receive no compensation. It seems to me that these kinds of misadventure have got to be coped with under the general framework of social insurance benefits rather than by a specific scheme for drugs that are on the market. If drugs are used in a clinical trial there must be a different mechanism, and here I side with Desmond Laurence.

Broadly speaking, I am optimistic about the future because I think it is clear that biological science is still in a period of extraordinarily rapid growth, and there are many areas, such as the control of cell growth and memory, about which we still know very little but which we shall know more about within a time scale of, say, 25 or 200 years. Our ability to influence those mechanisms, once we know about them, with drugs must be great and will be beneficial in some kinds of disease.

We must improve the predictability of treatment. That means better prediction of the people who require a particular drug. In my own field of hypertension, it cannot be right to treat 10 to 20 per cent of the adult population of Western countries with anti-hypertensive drugs. That would be ridiculous. The targeting of treatment must be improved in the future. But although I am optimistic that there will be great contributions coming from pharmacology in the future, I do not go along with Professor Joyce, who implied that everything will get easier and that medicines will be more like natural products and less toxic. I do not believe that will be so. Although we shall get cleverer, our own cleverness will lead to greater complexity because we are dealing with such a complex system. It is nevertheless a world which I approach with optimism because I am sure that the results in the long run will be beneficial.

GENERAL DISCUSSION

The contributions to the general discussion period of the final session of the symposium can perhaps best be recorded by linking them in with a series of observations made by Professor D. W. Vere (London Hospital Medical College). Professor Vere suggested that there might be at least four areas requiring clarification and attention if we are to expedite the progress of the Second Pharmacological Revolution.

The first concerns patient compliance. Professor Vere argued that patients' attitudes to drug usage of the past would be entirely inappropriate for the forthcoming wave of pharmacological advance. In his words, 'special attention should be given to cleaning up those misunderstandings which at present only occasionally lead to disaster and more often to discomfort but which, in the new era, will lead to quite terrific problems'.

His second point related to adverse drug reactions. There is a marked tendency to regard drugs in the same light as consumer durables, such as refrigerators or motor cars, which are susceptible to the development of faults. This is entirely inappropriate because the 'fault' – if fault there be – lies instead in the medicine consumer in the sense of either an unwitting

abnormality disclosed by the taking of a drug or an undesirable interaction between the drug and the user. This clearly places a premium on the accumulation and dissemination of information about the prescribing experience associated with a particular drug and, as discussed in the previous session, on a better understanding of the risk/benefit concept on the part of medicine consumers.

Professor Vere's third point concerned health expectations, What consumers want and press for depends on their 'health belief models', yet these are often faulty and ill-informed. Furthermore, it is extremely difficult to educate people to adopt more appropriate expectations. This suggests that whilst patients' views must be heard and discussed they should not be accorded uncritical acceptance.

Speaking from the perspective of general practice, one member of the audience commented that perhaps too much is heard of the responsibility *to* the consumer and not enough of the responsibility *of* the consumer. The view was expressed that patients generally harbour unrealistic expectations of what their general practitioners can do for them and that perhaps the various consumer groups could play their most valuable role in facilitating the benefits which might be expected to accrue from the Second Pharmacological Revolution by ensuring that patients' expectations are not set inappropriately high.

Responding to the comment Dame Elizabeth Ackroyd agreed that as a result of a variety of influences people nowadays have higher expectations, and not only in the context of medical treatment. And today people are more apt to talk about their rights than they were in earlier times. To match this development she suggested that family doctors ought perhaps to be more prepared to discuss matters with their patients than has tended to be the case in the past. It would seem reasonable to anticipate that improvements in intercommunication might help to temper expectations and reduce dissatisfaction reflected in, for example, demands for second opinions. On the whole, however, Dame Elizabeth Ackroyd concluded that most doctor/patient relationships, as evidenced by the work of Cartwright and her colleagues, appear to be satisfactorily managed.

Professor Vere's final point hinged on the implication of one of Dame Elizabeth Ackroyd's remarks that in some clinical trials the interests of the statisticians appear to have overshadowed those of the patients involved. Professor Vere considered that it needed to be made clear that the primary interest of the statistician is to disclose the truth and that the whole point of scientific method is that it aims to minimise the time taken and the suffering caused in the costly discovery of new knowledge. Unfortunately, that cost invariably impinges on a cohort of patients who 'turn up' at the time of a new drug discovery – but how can it be otherwise? Statistical investigation should most appropriately be seen as a valuable means of ultimately minimising the impact of disease on patients and not as a 'kind of hobby that researchers enjoy in a back room'.

(In relation to this last area of discussion, Dr Sankaran informed the audience that the World Health Organisation had recently finalised a document on the scientific quality of research on human subjects. This had been submitted to the Executive Board, and would be completed and published in a few months' time.)

In drawing the discussion period to a close, the chairman observed that 'if we plunge into the Second Pharmacological Revolution without working through the social implications we shall be swept away'. The task of creating a social environment favourably disposed to pharmacological innovation is fraught with difficulties. Not least it will require, as Professor Joyce observed, the industry further opening itself up to public examination and indulging in 'exercises in truth telling'. Such objectivity and truth telling must of course be pursued by all interested parties who must also show willingness to enter into constructive dialogue. Encouragingly, the evidence from this final session of the symposium suggests that positive moves are now being made in these directions.

Session chairmen, principal speakers and discussants

Dame ELIZABETH ACKROYD DBE has been Chairman of the Patients Association since 1978. She is Vice-Chairman of both the Waltham Forest Community Health Council and the London Voluntary Service Council. Amongst many other commitments, she is a Member of the Bedford College Council and Governor of Birkbeck College.

Dr RICHARD ARNOLD is the Director of the Association of the British Pharmaceutical Industry. Prior to this he was Commercial Manager of May & Baker's Pharmaceutical Division which he joined in 1959. He is a member of the Executive Committee of the European Federation of Pharmaceutical Industry Associations. He took a degree in chemistry at Nottingham University and undertook organic research in peptides for his PhD.

Professor RICHARD BATCHELOR is Professor of Immunology at the Royal Postgraduate Medical School, Hammersmith Hospital, London. His field of special interest is major histocompatibility systems and their role in transplantation and the control of immune responsiveness. He is the European co-editor of the journal 'Transplantation'.

Professor SUNE BERGSTRÖM is Professor of Chemistry at the Karolinska Institute, Sweden. He is Chairman of the Board of Directors of The Nobel Foundation and Chairman of the World Health Organisation's Advisory Committee on Medical Research. He is a member of numerous scientific societies, including the Royal Society of Edinburgh, the Indian National Science Academy and the Russian Medical Academy. He has published work in the fields of heparin, steroid and bile acid metabolism and the structures, isolation, biological action and clinical use of the prostaglandins. He was a joint winner of the 1982 Nobel Prize for Medicine.

Professor Sir JOHN BUTTERFIELD OBE became Regius Professor of Physic in the University of Cambridge in 1976 after serving as Professor of Medicine at Guy's Hospital and Vice-Chancellor of the University of Nottingham. In 1978 he was appointed Master of Downing College, Cambridge. He has served as a member of the Medical Research Council, as Chairman of the Medicines Commission and is also Chairman of the Stop Polio Campaign of the Save the Children Fund and a Trustee of the British Foundation for Age Research.

Mr PETER CUNLIFFE CBE is the President of the Association of the British Pharmaceutical Industry and Chairman of the Pharmaceuticals Division of Imperial Chemical Industries. He is a member of the Executive Committee of the European Federation of Pharmaceutical Industry Associations and is Vice-President of the International Federation of Pharmaceutical Manufacturers' Associations.

Professor HANS DENGLER is Director of the Medical Hospital and holds the Chair of Internal Medicine at Bonn University. Prior to this he was Director of the Outpatient Department of the Medical Hospital at the University of Giessen. He is the President of the German Association of Internal Medicine, a member of the New York Academy of Sciences, the German Pharmacological Society and the International Union of Pharmacology. He is the editor of and adviser to several European medical and pharmacological journals.

Professor COLIN DOLLERY has been Professor of Clinical Pharmacology at the Royal Postgraduate Medical School of London since 1969. He is also a consultant physician at both the Hammersmith and Ealing Hospitals. He has published many papers on the natural history of hypertension and the effect of drug treatment. His opinions about biomedical and health care research and the important role of pharmacology in the future of medicine were summarised in the Rock Carling Lecture he gave in 1978.

Mr LEWIS ENGMAN became President of the American Pharmaceutical Manufacturers' Association in 1979. He is also a member of the Council of the International Federation of Pharmaceutical Manufacturers' Associations. After practising law, following his graduation in both law and economics, he served on the White House staff as legislative and general counsel to the President's Special Assistant for Consumer Affairs. He was later appointed Assistant Director of the White House Domestic Council. From 1973–75 he was Chairman of the Federal Trade Commission.

The Rt Hon NORMAN FOWLER MP was appointed Secretary of State for Social Services in September 1981, having been Minister of Transport from 1979 and Secretary of State for Transport since January 1981. Prior to entering Parliament, he was Home Affairs Correspondent for *The Times*. He became Conservative MP for Nottingham South in 1970 and in 1976 was elected MP for Sutton Coldfield. During the previous Labour Government he held several posts as Opposition Spokesman, including Chief Opposition Spokesman on Social Services.

Professor RONALD GIRDWOOD FRSE is Vice-President of the Royal College of Physicians of Edinburgh and was until his recent retirement Professor of Therapeutics and Clinical Pathology at the University of Edinburgh. He is a member of the Committee on Safety of Medicines and the Medico-Pharmaceutical Forum and is Chairman of the Executive, Scottish National Blood Transfusion Association. He has edited four books, including one on clinical pharmacology, has written numerous papers and has lectured world-wide.

The EARL OF HALSBURY FRS has been Chancellor of Brunel University since 1966. From 1949 for ten years he was Managing Director of the National Research Development Corporation and was for 20 years on the Science Development Council and its predecessors. Amongst numerous other commitments, he has been a Member of the Medical Research Council, a Governor of the British Broadcasting Corporation, and is at present a Governor of the London School of Economics and the University of Manchester Institute of Science and Technology.

Dr ARTHUR HAYES JR was appointed Commissioner of Food and Drugs in the US Department of Health and Human Services in 1981. He joined the FDA from the Pennsylvania State University College of Medicine where, since 1972, he had served as Professor of Medicine and Pharmacology and as Chief of the Division of Clinical Pharmacology. He is a member of and holds fellowships in a large number of professional and scientific societies.

Dr WILLIAM HUBBARD JR is President of The Upjohn Company in the United States. In 1970 he concluded a 25 year academic career as Professor of Medicine and Dean of the Faculty at the University of Michigan. He is a member of The Institute of Medicine of the National Academy of Sciences and a Trustee of the W K Kellogg Foundation and of Columbia University.

Professor ROSALINDE HURLEY is Professor of Microbiology at Queen Charlotte's Maternity Hospital, London and is also the present chairman of the Medicines Commission. She is an authority on infectious disease in obstetrics and serves on numerous committees concerned with microbiology. Professor Hurley's current major research interests are the vertical transmission of hepatitis B virus and the relationship of cytomegalovirus to mental retardation.

Dr DICK JOYCE is Head of the Project Innovation Group at CIBA-GEIGY in Switzerland. He was formerly Reader in Psychopharmacology at the University of London and Joint Head of the Department of Pharmacology and Therapeutics at the London Hospital Medical College. He is the author and/or co-editor, jointly or alone, of five books and 100 papers, the majority of which are on psychopharmacological and ethical topics.

Professor ERICH KAUFER is Profesor of Economics at the University of Innsbruck. In 1965, having achieved his PhD in economics at Marburg University, he undertook post-graduate studies at Cornell University and the University of Michigan. In 1970–77 he was Professor of Economics at the University of Saarland. His main field of research has been in industrial economics, public regulation and competition policy. He has been the author of many books and articles and is the expert for health economics at the Mainz Academy of Sciences.

Mr SHINBEI KONISHI is the Chairman of Takeda Chemical Industries Limited and the Chairman of Lederle (Japan) Limited. He graduated from the Department of Pharmaceutical Sciences of the University of Tokyo.

Dr CHARLES MYERS is Chief of the Clinical Pharmacology Branch of the National Cancer Institute. He is a member of the American Association of Cancer Research, American Society of Clinical Investigation and American Association for the Advancement of Science. He is active as a Clinical Oncologist and has written or co-authored over 70 papers.

Mr OTTO NOWOTNY is an Economic Adviser for Hoffmann-La Roche in Switzerland. Having completed his studies in mechanical and aeronautical engineering at the Swiss Federal Institute of Technology, he worked in the Brazilian steel and Canadian aluminium industries and obtained his MBA from the Harvard Business School. He joined Roche in 1958.

Mr MICHAEL PERETZ MBE was appointed Executive Vice-President of the International Federation of Pharmaceutical Manufacturers' Associations in 1979. He is a pharmacist and worked for some years with the Boots Company where he was in charge of their international business. From 1967–78 he worked for the Cyanamid Company as Managing Director and later Chairman of their UK organisation. He was President of the Association of the British Pharmaceutical Industry from 1975–77.

Dr BALU SANKARAN is Director of the Division of Diagnostic, Therapeutic and Rehabilitative Technology at the World Health Organisation. Prior to taking up this post in 1981 he was Director-General of Health Services in India. Following his post-graduate training in the United States and England, appointments at the All India Institute of Medical Sciences and a two-year Rockefeller Foundation Fellowship at the University of Illinois, he was made Professor of Orthopaedic Surgery at the University of Delhi in 1967. In 1970 he became Director of India's Central Institute of Orthopaedics and Traumatology.

Mr DAVID TAYLOR has worked with OHE since 1972 and has been its Deputy Director since 1976. He has written over 40 major papers for the Office and has published some 200 other articles and papers. He has been Vice-Chairman of a Community Health Council for six years and is Vice-Chairman of the Governors of a school for mentally handicapped children. He has served as an advisor to a number of charities and the World Health Organisation.

Professor GEORGE TEELING SMITH OBE has been Director of the Office of Health Economics since its foundation in 1962. Prior to that he was Deputy Managing Director of the Winthrop company in Britain. He is Professor Associate in Health Economics at Brunel University.

Professor PETER TEMIN is Professor of Economics at the Massachusetts Institute of Technology. He has written extensively on economic history and health economics. His most recent book 'Taking Your Medicine: Drug Regulation in the United States' chronicles the development of modern drug regulation in the US in the context of theoretical considerations about choice under uncertainty.

LORD VAIZEY is an economist and writer. As well as being Principal of the King George VI and Queen Elizabeth Foundation, he is a director of a number of companies. He was a Fellow of St Catharine's College, a Fellow and Tutor of Worcester College and Professor of Economics at Brunel University. He is a member of the OHE Editorial Board.

Dr JOHN VANE FRS has been Group Director of Research and Development at The Wellcome Foundation since 1973. Prior to this, he was Professor of Experimental Pharmacology at the Institute of Basic Medical Sciences of the Royal College of Surgeons. His research has mainly centred on vasoactive hormones, such as catecholamines, peptides and prostaglandins. In 1976 he and his team at Wellcome discovered prostacyclin. He was a joint winner of the 1982 Nobel Prize for Medicine.

Dr STUART WALKER is the Director of the Centre for Medicines Research. Before joining the Medical Division of Glaxo Group Research as Senior Clinical Research Adviser and Unit Head in 1973, he lectured in Clinical Pharmacology at the Cardiothoracic Institute, London University. He became the first Director of the CRM in 1981 and is currently undertaking studies to determine the factors influencing innovation and drug development and the rational basis for safety evaluation of medicines and the predictive value of animal toxicity tests.

Dr WILLIAM WARDELL is Associate Professor of Pharmacology, Toxicology and Medicine and Director of the Center for the Study of Drug Development at the University of Rochester School of Medicine and Dentistry. After achieving his medical qualifications in New Zealand and England, he went to the United States in 1970 on a Merck International Fellowship in Clinical Pharmacology before taking up his present position. He is Chairman of the Committee on Government Affairs of the American Society for Clinical Pharmacology and Therapeutics and Chairman of the Committee on Drug Development.

Professor Sir BRUCE WILLIAMS KBE is the Director of The Technical Change Centre. From 1967–81 he was the Vice-Chancellor of the University of Sydney. Prior to that he was the Professor of Political Economy at the University of Manchester. He has written extensively on technical change and economic growth.

Dr ARNOLD WORLOCK is Group Marketing Director of the Wellcome Foundation. He worked previously with Hoechst AG and was Chairman of Hoechst UK Pharmaceuticals. He is Chairman of the European Federation of Pharmaceutical Industries Association Working Party on Health Care Regulation and Registration, a member of the Association of the British Pharmaceutical Industry's International Committee, and Chairman of an independent European research-based Industry Group on relations with Third World and Supranational Organisations.

Index